



## Increased frequency of microalbuminuria in patients with type 3 autoimmune polyglandular syndrome (APS) compared to isolated autoimmune type 1 diabetes mellitus: A real-life study

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### ABSTRACT

**Aim of the study:** The primary aim of the study was to evaluate the differences in metabolic control and chronic microvascular complications in patients with type 3 autoimmune polyglandular syndrome (APS3), compared to type 1 diabetes mellitus (T1DM) alone. Secondary aims were to evaluate the age of autoimmune thyroid disease (AIT) onset and the effects of levothyroxine treatment on metabolic control in patients with APS3.

**Material and methods:** We retrospectively reviewed 276 patients with T1DM alone and 214 patients with APS3 and evaluated clinical and metabolic parameters and microvascular complications.

**Results:** Patients with T1DM showed a longer duration of diabetes ( $p = 0.001$ ) and lower age of diabetes onset ( $p = 0.020$ ) compared to patients with APS3. Female gender ( $p = 0.001$ ) and microalbuminuria ( $p = 0.006$ ) were significantly more frequent in patients with APS3 compared to T1DM. In addition, patients with APS3 showed higher AIT onset frequency in the 16–30 quartile age-range. Furthermore, APS3 patients treated with levothyroxine showed significantly better HbA1c values than non-treated patients ( $p = 0.001$ ).

**Conclusions:** We found that patients with APS3 showed positive microalbuminuria, earlier than T1DM. Patients with APS3 showed higher frequency of AIT age of onset in the 16–30 age-range and those treated with levothyroxine had better metabolic control, than untreated ones.

### 1. Introduction

Autoimmune polyglandular syndromes (APS) are characterized by a combination of at least two autoimmune endocrinopathies [1]. Type 1 APS is very rare and is characterized by a triad of mucocutaneous candidiasis, hypoparathyroidism, and autoimmune Addison's disease [2,3]. Type 2 APS occurs in middle age and is characterized by the presence of autoimmune Addison's disease combined with autoimmune thyroid disease (AIT) and/or type 1 diabetes mellitus (T1DM) [4]. Up to one third (15–30 %) of patients with T1DM have autoimmune thyroid disease, Hashimoto's thyroiditis or Graves' disease, clustering type 3 APS [1,5,6].

Epidemiological studies have documented the incidence and prevalence of APS in the paediatric population [5,6], while less evidence is

available regarding the incidence and prevalence of APS3 in the adult population with T1DM. It is well known that the presence of AIT and T1DM requires complex management of the patient due to the effect of thyroid hormones on metabolic control and insulin requirement [7,8]. Among the factors involved, metabolic control appears to play an important role in the development of micro- and macrovascular disease in T1DM, with a great impact on mortality [9,10]. By contrast, the impact of AIT on the risk of chronic complications of T1DM needs to be clarified.

The primary aim of the study was to evaluate the differences in metabolic control and chronic microvascular complications in patients with APS3, compared to T1DM alone. Secondary aims were to evaluate the age of onset of AIT and the effects of levothyroxine treatment on metabolic control in the group of patients with APS3.

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## 2. Material and methods

This study retrospectively included a population of 490 adult outpatients with T1DM diagnosed for at least 5 years, followed at the Endocrinology and Metabolism Division of the University Hospital of Palermo from December 2017 to December 2022. Patients were divided into two groups: group A included patients with T1DM alone (n = 276) and group B included patients with APS3a (n = 214) based on the presence of combined Hashimoto's thyroiditis and T1DM.

The exclusion criteria were the following: presence of a third autoimmune disease, pregnancy, hypoglycaemia unawareness, acute illnesses or infections, inability to provide informed consent, duration of thyroid disease less than 3 years and duration of diabetes less than 5 years, age <18 years, presence of hyperthyroidism or Graves' disease, presence of overt hypothyroidism (TSH values > 10  $\mu$ IU/ml). For all patients we evaluated age, gender, body mass index (BMI), thyroid function in terms of thyroid stimulating hormone (TSH) values, glycosylated haemoglobin (HbA1c), insulin requirement (IR), type of glucose monitoring (Self-Monitoring Blood Glucose SMBG or Flash Monitoring Glucose FMG) and insulin treatment modality (Multi Daily Injections MDI or Continuous Subcutaneous Insulin Infusion CSII). The insulin requirement was calculated as total daily dose per kg of body weight.

We also evaluated the frequency of diabetic chronic microvascular complications including retinopathy classified as absent, non-proliferating and proliferating and nephropathy evaluated by creatinine measurement and estimated glomerular filtrate rate (GFR), calculated according to CKD-EPI formula, and microalbuminuria (positive definite for values > 30 mg/g in at least two consecutive measurements). The categories of diabetic kidney disease were based on the current classification provided by the US National Foundation Kidney Disease Outcomes Quality Initiative (NFK-KDOQI) [11].

The diagnosis of APS-3 was based on clinical symptoms and serological testing [12]. Type 1 diabetes mellitus was diagnosed in agreement with the American Diabetes Association guidelines [13] and HT was diagnosed by the presence of antibodies against thyroid peroxidase (TPO antibodies) confirmed in two different determination with associated typical ultrasonography pattern [14]. The patients with absence of TPO-antibodies but with ultrasonography pattern diagnostic for HT were excluded.

To evaluate the age of AIT onset in patients with APS3, we stratified patients into quartiles, 0–15 years, 16–30 years, 31–45 years and over 45 years.

To evaluate the effects of levothyroxine on metabolic control, we divided patients with APS3 into two groups: group A, which included patients with hypothyroidism treated with levothyroxine (N = 101 patients, 47.4%), and group B, which included patients with euthyroidism or subclinical hypothyroidism not pharmacologically treated (N = 113 patients, 52.6%).

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Approval was obtained from the Ethics Committee of the University of Palermo. At the time of hospitalization, an informed consent for the scientific use of the data was obtained from all patients to be included in the study.

### 2.1. Assays

Glycaemia, HbA1c, creatinine and lipids were measured by standard methods (Modular P800, Roche, Milan). LDL-C levels were measured using the Friedewald formula [TC - (HDL + (TG/5))]. Estimated glomerular filtrate rate (GFR) was calculated according to CKD-EPI equation.

### 2.2. Statistical analysis

Continuous variables are expressed as mean  $\pm$  standard deviation (SD). The normality of distribution of the quantitative variables was assessed using the Kolmogorov-Smirnov test. Categorical variables are reported as rates and proportions. The differences between variables were evaluated with t-Student for quantitative ones and  $\chi^2$  for trend for categorical ones. A p value < 0.05 is considered statistically significant. The statistical analysis was performed with MedCalc  $\copyright$  software.

## 3. Results

The clinical, anthropometric and metabolic parameters of the patients are shown in Table 1. No significant differences were found for age, BMI, TSH, IR, metabolic parameters, insulin therapy and glucose monitoring between the two groups. Patients with T1DM alone showed a longer duration of diabetes (p = 0.001) and lower age of diabetes onset (p = 0.020) compared to patients with APS3. Female gender was significantly more frequent in the group of patients with APS3 compared to T1DM alone (p = 0.001) (Table 1). In addition, patients with APS3 showed a significantly higher frequency of microalbuminuria than patients with T1DM (p = 0.006) (Table 2). With regard to the sub-analysis in patients with APS3, we found higher frequency of AIT onset in the 16–30 quartile age-range (50.7%) (Fig. 1). Furthermore, the patients treated with levothyroxine showed significantly better HbA1c values than patients not treated with levothyroxine (p = 0.001) (Fig. 2).

**Table 1**

Clinical and metabolic parameters of patients with isolated T1DM compared with APS3.

	Total (n = 490) Mean $\pm$ SD	T1DM (n = 276) Mean $\pm$ SD	APS 3 (n = 214) Mean $\pm$ SD	p
Age (years)	41.3 $\pm$ 13.4	41.7 $\pm$ 13.0	40.7 $\pm$ 13.9	0.990
Duration of diabetes (years)	21.0 $\pm$ 12.4	22.6 $\pm$ 12.5	19.0 $\pm$ 11.9	0.001
Age of onset of Diabetes (years)	20.1 $\pm$ 11.6	19.0 $\pm$ 11.2	21.5 $\pm$ 12.0	0.020
HbA1c (%)	7.9 $\pm$ 1.3	7.9 $\pm$ 1.3	8.0 $\pm$ 1.4	0.500
IR (U/kg)	1.61 $\pm$ 0.62	0.6 $\pm$ 0.2	0.6 $\pm$ 0.2	0.400
BMI (kg/m <sup>2</sup> )	24.1 $\pm$ 3.7	24.5 $\pm$ 3.7	24.0 $\pm$ 3.7	0.100
eGFR	101.8 $\pm$ 20.4	102.2 $\pm$ 20.9	101.3 $\pm$ 19.8	0.600
TSH	2.2 $\pm$ 0.59	2.30 $\pm$ 0.55	2.35 $\pm$ 0.63	0.590
	<b>Subjects (%)</b>	<b>Subjects (%)</b>	<b>Subjects (%)</b>	
Gender				<0.001
Male	234 (74.8%)	170 (61.6%)	64 (29.9%)	
Female	256 (52.2%)	106 (38.4%)	150 (70.1%)	
Glucose monitoring				0.930
SBMG	305 (62.2%)	171 (62%)	134 (62.6%)	
FGM	185 (37.8%)	105 (38.0%)	80 (37.4%)	
Insulin therapy				0.600
MDI	440 (89.8%)	246 (86.1%)	194 (89.8%)	
CSII	50 (10.2%)	30 (10.9%)	20 (10.2%)	

Abbreviations: T1DM: type 1 diabetes mellitus; APS3: autoimmune polyglandular syndrome type 3; IR: insulin requirement; GFR: glomerular filtration rate; SBMG: self blood glucose monitoring; FGM: flash glucose monitoring; MDI: multiple daily injections; CSII: continuous subcutaneous insulin infusion.

**Table 2**  
Chronic complications of patients with isolated autoimmune T1DM vs T1DM in APS3.

	Total (n = 490) Subjects (%)	T1DM (n = 276) Subjects (%)	APS 3 (n = 214) Subjects (%)	p
Microalbuminuria				0.006
Negative	432 (88.2%)	253 (91.7%)	179 (83.6%)	
Positive	58 (11.8%)	23 (8.3%)	35 (16.4%)	
CKD				0.205
G0	377 (76.9%)	219 (79.3%)	158 (73.8%)	
G1	97 (19.8%)	46 (16.7%)	51 (23.8%)	
G2	10 (2.0%)	7 (2.5%)	3 (1.3%)	
G3-G4	6 (1.2%)	4 (1.5%)	2 (0.9%)	
Retinopathy				0.6
Absent	370 (75.5%)	205 (74.3%)	165 (77.1%)	
Non proliferating	79 (16.1%)	45 (16.3%)	34 (15.9%)	
Proliferating	41 (8.4%)	26 (9.4%)	15 (7.0%)	

Abbreviations: T1DM: type 1 diabetes mellitus; APS3: autoimmune polyglandular syndrome type 3; CKD: chronic kidney disease.

**4. Discussion**

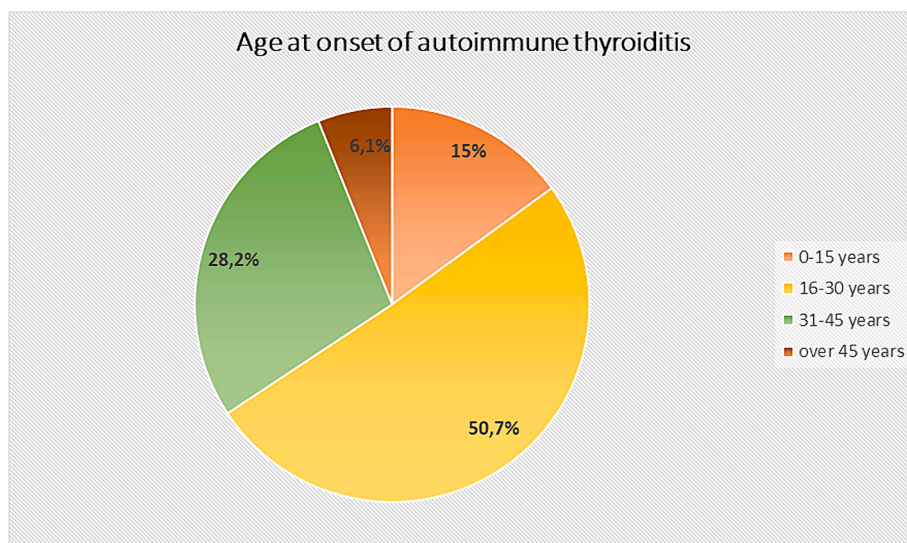
In the current study we aimed to evaluate the differences in metabolic control and chronic microvascular complications in patients with APS3, characterized by combined AIT and T1DM, compared to isolated

T1DM, and found no differences in terms of metabolic control evaluated through HbA1c and glycaemic values. Interestingly, we found that patients with APS3 had higher frequency of microalbuminuria than T1DM alone. In addition, we found a peak of incidence of AIT in younger patients, in the quartile 16–30 years, and better metabolic control in those patients with APS3 who were treated with levothyroxine compared with those who were not treated.

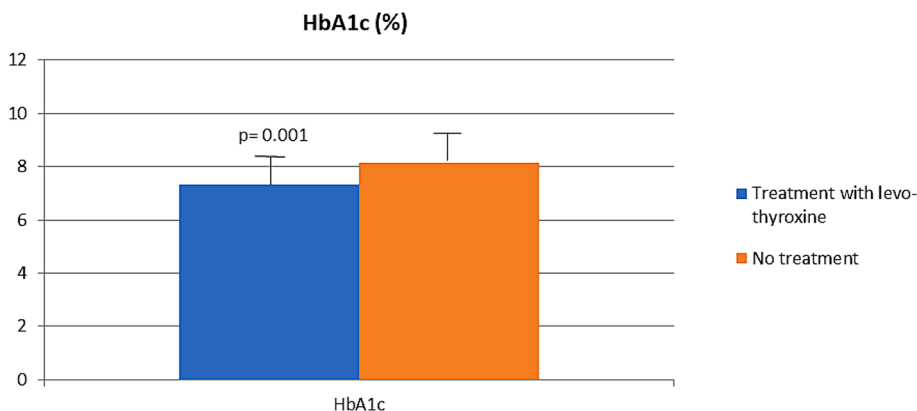
The relationship between AIT and T1DM is complex and bidirectional [15–17]. Several epidemiological studies have documented a higher prevalence of AIT (about 15–30%) in children and adolescents with T1DM [18–20].

Our results are in agreement with other studies documenting an increased risk of developing AIT in patients with T1DM aged > 6 years [21–23]. On the other hand, several studies have documented how overt hypothyroidism negatively affects the metabolic control and the BMI of patients with both type 1 and type 2 diabetes mellitus [24–26]. In our study the presence of Hashimoto’s thyroiditis does not seem to influence metabolic control and body weight, as demonstrated by the comparable HbA1c and BMI values in patients with isolated T1DM and APS3. However, levothyroxine therapy is associated with a better metabolic control, in terms of HbA1c values, in the subgroup of patients with APS3 compared to patients not treated with levothyroxine.

Our findings may suggest that it is not the simple association with thyroid autoimmunity but the presence of hypothyroidism that leads to worse metabolic control in patients with APS3, in agreement with other



**Fig. 1.** Distribution of patients with APS3 in four quartiles according to age of onset of autoimmune thyroiditis.



**Fig. 2.** HbA1c values in patients with APS3, divided in two groups, treated and not treated with levothyroxine.

studies that have shown that hypothyroidism causes increased BMI, resulting in macro- and microvascular complications in patients with T1DM [27,28]. However, to date few studies have considered the potential influence of AIT in the development of chronic microvascular complications in patients with T1DM. In our study we found a frequency of retinopathy of 24.5 % and of chronic kidney disease of 23 %. While the risk of developing retinopathy and chronic kidney disease was not influenced by the presence of AIT, patients with combined Hashimoto's thyroiditis and T1DM had a significantly higher frequency of microalbuminuria than patients with isolated autoimmune TDM1. This finding did not appear to be influenced either by metabolic control or by the duration of diabetes, which was also greater in patients with isolated T1DM. Wei Zhu et al. documented a significantly positive correlation between the presence of anti-TPO antibodies and microalbuminuria in adult patients with newly diagnosed T2DM, regardless of metabolic control and BMI [29]. In patients with T1DM the presence of HT should be screened, especially in the paediatric and adolescent ages. In this population of patients, HT should be treated with levothyroxine, also for subclinical hypothyroidism, as this determines better metabolic control. In adults with T1DM the presence of thyroiditis seems to determine a greater risk of developing microalbuminuria, even though the underlying mechanisms still need to be clarified.

In conclusion, in the current study we found that patients with APS3 show positive microalbuminuria, earlier than patients with T1DM alone. Patients with APS3 show a higher frequency of AIT age of onset in the 16–30 years age-range and those treated with levothyroxine have better metabolic control, evaluated by HbA1c levels, than those not treated. However, further controlled studies on a larger population are required to confirm our preliminary data.

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## CRediT authorship contribution statement

**Stefano Radellini:** Writing – original draft, Supervision, Investigation, Formal analysis, Data curation, Conceptualization. **Enrica Vigneri:** Investigation, Conceptualization. **Ornella Ferreri:** Investigation, Data curation. **Piero Luigi Almasio:** Investigation. **Giuseppe Pizzolanti:** Investigation. **Carla Giordano:** Writing – review & editing, Writing – original draft, Supervision. **Valentina Guarnotta:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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