Comorbid autoimmune diseases and burden of diabetes-related complications in patients with type 1 diabetes from a Mediterranean area

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ABSTRACT

Aim: To assess the prevalence of autoimmune diseases (AID) in patients with type 1 diabetes (T1D) and to evaluate whether the rate of diabetes-related complications differs depending on the presence of AID.
Methods: Cross-sectional analysis of 13,570 T1D patients aged $\geq$ 18 years registered in the SIDIAP database. The association between AID and diabetes-related complications was assessed by multivariable logistic regression models.
Results: The prevalence of AID was 18.3% with thyroid AID being the most common. Patients with T1D and AID were more often female and their current age, age of diabetes onset and diabetes duration were higher. Patients with only thyroid AID experienced a lower risk of peripheral artery disease (odds ratio [OR] = 0.51, 95%; confidence interval [CI] 0.31 to 0.81) and kidney disease (OR = 0.68, 95%; 95% CI 0.54 to 0.85), whereas patients with other AID had an increased risk of ischemic heart disease (OR = 1.48, 95%; 95% CI 1.04 to 2.06).
Conclusions: The burden of diabetes-related complications in patients with T1D differs according to the type of additional AID. The presence of diabetes complications is lower in those with autoimmune thyroid disease while the presence of other AID is associated with higher rates of ischemic heart disease.

1. Introduction

Type 1 diabetes (T1D) is a frequent autoimmune disease (AID) with and estimated prevalence of 9 million people worldwide [1]. T1D is characterized by the destruction of pancreatic islet β-cells that leads to the need for lifelong treatment with insulin. Patients with T1D are exposed to an increased risk for microvascular and macrovascular complications and to a considerable disease-related distress [2]. The prevalence of other AIDs in T1D patients, either endocrine or non-endocrine, is high [3,4,5], adding morbidity and treatment complexity to a people already under significant disease associated burden [6]. The

epidemiology and risk factors for microvascular and macrovascular complications in T1D patients have been extensively studied [7,8,9], but less attention has been paid to the presence of comorbid AIDs and their impact on the presence of complications. Additional autoimmune diseases may negatively affect metabolic control in patients with T1D [10,11], thereby potentially increasing the risk of micro or macro-vascular complications. Furthermore, most autoimmune diseases confer an increased risk of cardiovascular disease [12,13], which could add to the already high baseline cardiovascular risk of T1D. Existing data on this matter are controversial, showing either a higher [14] or lower [15] prevalence of cardiovascular disorders related to the presence of

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additional AIDs in patients with T1D. Furthermore, the prevalence of microvascular complications in the presence of additional AIDs shows conflicting results [16,17].

The largest studies that have characterized different aspects of patients with T1D and concomitant AIDs come from North America [4,14,15], Northern Europe [5] and Germany-Austria [17]. However, the prevalence of AIDs and their co-existence with T1D may be subject to geographical differences [18] and, to our knowledge, so far no studies have been performed on the relationship between T1D and its chronic complications with other AIDs in the Mediterranean area.

To address this gap, we aimed to evaluate in a well-characterized population of T1D adult patients [19] from a Mediterranean area, i.e. Catalonia (Northern Spain): 1) the prevalence of additional AIDs, and 2) whether the rate of diabetes complications differs depending on the presence of additional AIDs.

2. Materials and methods

This was a retrospective cross-sectional study of patients with T1D registered in the SIDIAP database [20]. A detailed description of the SIDIAP database and how T1D patients were identified in the database has recently been published [19]. Briefly, SIDIAP is a primary healthcare database which captures anonymized information of approximately 5.8 million people in Catalonia registered with a family physician from the Institut Català de la Salut (ICS, Catalan Institute of Health). ICS provides primary health care to around 75% of the Catalan population that is representative of all the Catalonia's population in terms of geography, age, and sex. Although, patients with T1D are usually attended at the specialist care setting bound to a hospital facility, prescriptions of chronic treatments and glucose control materials are provided at the primary care centres, guaranteeing that regardless of where clinical care is provided, the registry of patients with T1D of any age by the ICS and CatSalut databases can be considered complete. SIDIAP includes data from the common primary care electronic medical records (demographics, diagnoses, clinical variables, prescriptions, referrals and laboratory results). It also includes medications dispensed in pharmacy offices and incorporates data of hospital discharges obtained from the Basic Minimum Set of Data (BMSD). The SIDIAP database has previously been used to conduct several observational studies that evaluate clinical characteristics and outcomes in Type 1 [19,21] and Type 2 [22,23] diabetes in Catalonia.

We retrieved data from subjects older than 18 years with a registered diagnosis of T1D (International Classification of Diseases 10 [ICD-10] code E10) prior to January 1, 2017 with no concomitant diagnosis of other types of diabetes (E11, E13, E14). To refine the patient selection, we applied restrictive criteria by excluding patients with an E10 diagnosis treated with glucose-lowering agents other than insulin and those who were not treated with short acting insulins more than two years after the registered date of diagnosis. These restrictive criteria were based on records of medications retrieved at pharmacies during the data collection period from January 1, 2016 through December 31, 2016, thus limiting the cross-sectional cohort to patients who had contacted the ICS system during this period. If not otherwise stated, the last registered measure during the year 2016 was recorded. Data collected for the present analysis included age, sex, duration of diabetes (2016 minus year of diabetes diagnosis), HbA1c (mean of all values available during the study period), estimated glomerular filtration rate (GFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula, and urinary albumin/creatinine ratio. Registered diagnosis of T1D complications were retrieved using ICD-10 codes as previously described [19] **(Supplementary** Table 1). Additionally, registered codes for autoimmune diseases were retrieved as specified in Supplementary Table 2.

The study was approved by the Ethics Committee of the Primary Health Care University Research Institute Jordi Gol (approval number: P17/115, date of approval: 07/06/2017).

2.1. Statistical analysis

Descriptive statistics were performed to summarize the sociodemographic characteristics of the study population, as well as the study variables (clinical, comorbidities and autoimmune diseases).

Descriptive data were calculated for the total population according to the absence/presence of any autoimmune disease.

Owing to the high prevalence of thyroid disease in the study population, autoimmune disease was treated as a 3-category factor: none, thyroid autoimmune disease only and other autoimmune disease (regardless of the presence of thyroid autoimmune disease).

Differences between categorical and quantitative variables were analyzed using compareGroups R package [24].

Multivariate logistic regression models were performed with macrovascular complications (ischemic heart disease, cerebrovascular disease, and peripheral artery disease) and microvascular complications (retinopathy, neuropathy, and kidney disease) as response variables. Statistically significant variables with a value of $p < 0.05$ in the univariate analysis, and those variables that were considered relevant, were included in the multivariate models. Prevalences and Odds ratio (OR) estimations were expressed with confidence interval 95% (95 %CI).

Statistical analyses were performed using R software for Windows version 3.6.1 [25].

3. Results

The final sample consisted of 13,570 cases with T1D aged 18 years or over (mean age ± SD, 45.2 ± 15.3 years). Sex distribution was 7,745 (57.1%) men and 5,826 (42.9%) women. Mean ± SD age at diagnosis was 31.7 ± 16.5 years, with a mean duration of diabetes of 14.1 ± 9.9 years.

3.1. Additional AIDs according to clinical characteristics

The prevalence of additional autoimmune disease in this study population was 18.3% (95% CI 17.6% to 18.9%). The mean time since diagnosis of additional AID was significantly shorter than that of T1D (8.0 ± 6.6 vs 14.1 ± 9.9; p < 0.001).

Patients with T1D and additional AID were more often female and their current age, age of diabetes onset and diabetes duration were higher than those without additional AID. (Table 1).

Regarding the group of patients with autoimmune disease, 89.5% (2,225) had only one additional AID disease, whereas we found 239 (9.6%) patients with 2 additional AIDs, and 21 (0.8%) with 3 or more additional AIDs.

Again, patients with more than one AID were more often female (71.1%), and were currently older (49.7 ± 15.5 vs 45.2 ± 15.3 years in those without AID), with an older age at diagnosis (34.2 ± 17.2 vs 31.7 ± 16.5 years) and a longer duration of diabetes (16.1 ± 11 vs 14.1 ± 9.9).

Table 2 shows the prevalence of autoimmune diseases grouped according to the organ or system affected and the most prevalent disease in each group. The most prevalent autoimmune disease was hypothyroidism that was clearly more prevalent in women. In the rest of AIDs with a prevalence sufficient to show differences, this was again higher in women except for "diseases of the skin and subcutaneous tissue" where no differences were observed.

3.2. Additional AIDs glycemic control and diabetes complications

Table 1 also shows the frequency of diabetes-related complications of T1D patients according to the presence of additional AIDs. Furthermore, patients with additional AID are separated in two groups according to the presence of only thyroid autoimmune disorders or other AIDs (whether or not with thyroid disease). Glucose control, reflected by mean HbA1c levels during the study year, showed significant, but

Table 1

Clinical characteristics and prevalence of micro- and macrovascular complications according to the presence of autoimmune diseases[1].

	All Population n = 13,571 (100%)	Without AID n = 11,086 (81.7%)	With any AID n = 2,485 (18.3%)	With only Thyroid AI disease n = 1,374 (10.1%)	With another AID[2] n = 1,111 (8.2%)
Female, n (%)	5,826 (42.9)	4,276 (38.6)	1,550 (62.4)[a]	969 (70.5)[a]	581 (52.3)[a]
Age (years)	45.2 (15.3)	44.6 (15.2)	47.8 (15.6)[a]	46.9 (15.1)[a]	48.9 (16.1)[a]
Age of diabetes diagnosis (years)	31.7 (16.5)	31.3 (16.3)	33.2 (17.3)[a]	32.2 (16.6)	34.4 (18.1)[a]
Diabetes duration (years)	14.1 (9.9)	13.8 (9.7)	15.2 (10.5)[a]	15.3 (10.6)[a]	15.1 (10.5)[a]
Stratified diabetes duration[b]					
≤ 10 years, n (%)	4,850 (35.7)	4,038 (36.4)	812 (32.7)	438 (31.9)	374 (33.7)
11 – 20 years, n (%)	6,264 (46.2)	5,142 (46.4)	1,122 (45.2)	627 (45.6)	495 (44.6)
21 – 30 years, n (%)	1,397 (10.3)	1,096 (9.8)	301 (12.1)	174 (12.7)	127 (11.4)
31 – 40 years, n (%)	657 (4.8)	499 (4.5)	158 (6.3)	84 (6.1)	74 (6.6)
≥ 41 years, n (%)	403 (2.9)	311 (2.8)	92 (3.7)	51 (3.7)	41 (3.6)
Smoking (yes)[3], n (%)	6,895 (50.8)	5,724 (51.6)	1,171 (47.1)[a]	639 (46.5)[a]	532 (47.9)[a]
HbA1c[4] (%)	8.1 (1.5)	8.1 (1.5)	8.0 (1.3)[c]	8.0 (1.3)[b]	7.9 (1.3)[b]
HbA1c[4] (mmol/mol)	65 (12)	65 (12)	64 (10)[c]	64 (10)[b]	63 (10)[b]
HbA1c[4]					
< 7% (53 mmol/mol) n (%)	1,767 (20.7)	1,426 (20.6)	341 (20.9)	178 (19.8)	163 (22.3)
≥ 7% (53 mmol/mol) n (%)	6,786 (79.3)	5,497 (79.4)	1289 (79.1)	720 (80.2)	569 (77.7)
Retinopathy, n (%)	2,977 (21.9)	2,401 (21.7)	576 (23.2)	304 (22.1)	272 (24.5)[b]
Albuminuria > 30 mg/g[5], n (%)	919 (14.3)	760 (14.6)	159 (12.9)	67 (9.7)[b]	92 (16.9)
Impaired renal function[6], n (%)	682 (9.6)	537 (9.4)	145 (10.3)	76 (9.7)	69 (11.1)
Kidney disease[7], n (%)	1,485 (25.8)	1,201 (26.1)	284 (24.7)	134 (20.8)[c]	150 (29.5)
Neuropathy, n (%)	1,046 (7.7)	829 (7.4)	217 (8.7)[c]	111 (8.0)	106 (9.5)[b]
Ischemic heart disease, n (%)	668 (4.9)	513 (4.6)	155 (6.2)[b]	75 (5.4)	80 (7.2)[a]
Cerebrovascular disease, n (%)	488 (3.6)	392 (3.5)	96 (3.8)	38 (2.7)	58 (5.2)[c]
Peripheral artery disease, n (%)	609 (4.4)	509 (4.5)	100 (4.0)	38 (2.7)[b]	62 (5.5)
Statin use n (%)	4353 (32.1)	3,422 (30.9)	931 (37.5)[a]	512 (37.3)[a]	419 (37.7)[a]
Antihypertensive drugs use (%)	4069 (30.0)	3,251 (29.3)	818 (32.9)[a]	420 (30.6)	398 (35.8)[a]

[1] Data are n (%), mean (SD) or median[IQR].

[2] Patients with AIDs excluding patients with only Thyroid AI disease;

[3] Either ex-smoker or current smoker.

[4] Available for 6,913 patients.

[5] Available for 6,426 patients.

[6] CKD-EPI < 60 ml/min, available for 7,104 patients.

[7] Includes albuminuria and/or impaired renal function and/or recorded diagnosis of Type 1 diabetes with renal complications (E10.2);

[a] p < 0.001 vs. T1D without AID.

[b] p < 0.005 vs. T1D without AID.

[c] p < 0.05 vs. T1D without AID.

Table 2

Prevalence of autoimmune diseases patients with type 1 diabetes ≥ 18 years of age according to sex[1].

	All population n = 13,571 (100.0%)	Males n = 7,745 (57.1%)	Females n = 5,826 (42.9%)	P-Value
Any AID	2,485 (18,3)	935 (12.1)	1550 (26.6)	
Thyroid gland disorders	1,592 (11.7)	466 (6.0)	1,126 (19.3)	< 0.001
Hypothyroidism or chronic autoimmune thyroiditis	1,388 (10.2)	404 (5.2)	984 (16.9)	< 0.001
Hyperthyroidism	146 (1.0)	46 (0.5)	100 (1.7)	< 0.001
Addison's disease	21 (0.1)	8 (0.1)	13 (0.2)	0.124
Autoimmune polyglandular failure	3 (0.0)	2 (0.0)	1 (0.0)	1.000
Primary ovarian failure	0 (0.0)	0 (0.0)	0 (0.0)	.
Diseases of the nervous system	66 (0.4)	26 (0.3)	40 (0.6)	0.005
Multiple sclerosis	50 (0.3)	19 (0.2)	31 (0.5)	0.010
Gastrointestinal disease	411 (3.0)	172 (2.2)	239 (4.1)	< 0.001
Celiac disease	219 (1.6)	83 (1.0)	136 (2.3)	< 0.001
Chronic atrophic gastritis and/or pernicious anemia	132 (0.9)	49 (0.6)	83 (1.4)	< 0.001
Ulcerative colitis	46 (0.3)	30 (0.3)	16 (0.2)	0.333
Liver and biliary tract disease	17 (0.1)	9 (0.1)	8 (0.1)	0.921
Primary sclerosing cholangitis	13 (0.1)	8 (0.1)	5 (0.1)	0.964
Diseases of the skin and subcutaneous tissue	526 (3.8)	288 (3.7)	238 (4.0)	0.294
Psoriasis	370 (2.7)	209 (2.7)	161 (2.7)	0.860
Vitiligo	165 (1.2)	86 (1.1)	79 (1.3)	0.225
Diseases of the musculoskeletal system and connective tissue	132 (0.9)	44 (0.5)	88 (1.5)	< 0.001
Rheumatoid arthritis	65 (0.4)	23 (0.3)	42 (0.7)	0.001

Data are n (%); 1 Grouped according to organ/system affected and the most prevalent in each group.

clinically non-relevant differences between groups and, in any case, it was slightly better in patients with additional AIDs who also showed a lower prevalence of smoking (either ex-smoker or current smoker).

Patients with any AID showed a higher prevalence of ischemic heart disease (23.2%) with a 95% confidence interval of 20.1% to 26.5%. However, this difference was not significant in the logistic regression analysis adjusted for age, sex, diabetes duration, dyslipidemia, hypertension and smoking (OR = 1.31; 95% CI 1.00–1.70; p = 0.050; **Supplementary** Table 3).

Patients with only thyroid autoimmune disorders showed a significantly lower prevalence of kidney disease and peripheral artery disease. In contrast, patients with other AID (excluding patients with only thyroid autoimmune disorders) showed a higher prevalence of retinopathy, neuropathy, ischemic heart disease and cerebrovascular disease.

In the logistic regression analysis, after adjusting for age, sex, diabetes duration, dyslipidemia, hypertension, smoking and kidney disease, the presence of autoimmune diseases, excluding patients with thyroid autoimmune disorders only, was associated with a higher likelihood of ischemic heart disease (p for trend, 0.025; Table 3), with all the other variables highlighted in the bivariate analysis losing significance (Tables 3, 4). In the group of patients with only thyroid autoimmune disease, after the logistic regression analysis, the lower odds of peripheral vascular disease and nephropathy persisted (p for trend, 0.006 and 0.001; Tables 3, 4).

Table 3
Multivariable logistic regression model for macrovascular complications.

Covariates	Ischemic heart disease			Cerebrovascular disease			Peripheral artery disease		
	Odds ratio	95 %CI	P-Value	Odds ratio	95 %CI	P-Value	Odds ratio	95 %CI	P-Value
No autoimmune disease (reference)	–	–		–	–		–	–	
Only thyroid AI disease	1.14	0.78 to 1.63	0.478	1.10	0.72 to 1.65	0.643	0.51	0.31 to 0.81	0.006
Other AID[1]	1.48	1.04 to 2.06	0.025	1.36	0.94 to 1.98	0.117	1.26	0.88 to 1.79	0.197
Sex (reference = male)	0.66	0.52 to 0.85	0.001	0.57	0.43 to 0.76	< 0.001	0.54	0.42 to 0.70	< 0.001
Age (years)	1.05	1.04 to 1.06	< 0.001	1.05	1.04 to 1.06	< 0.001	1.04	1.03 to 1.05	< 0.001
Diabetes duration (reference ≤ 10 years)	–	–		–	–		–	–	
Diabetes duration: 11 – 20 years	0.98	0.76 to 1.27	0.884	0.98	0.73 to 1.31	0.880	0.90	0.69 to 1.17	0.425
Diabetes duration: 21 – 30 years	0.70	0.43 to 1.09	0.129	1.06	0.66 to 1.66	0.804	1.05	0.69 to 1.57	0.807
Diabetes duration: 31 – 40 years	1.67	1.08 to 2.53	0.018	1.52	0.92 to 2.43	0.087	1.15	0.70 to 1.82	0.568
Diabetes duration: ≥41 years	2.01	1.33 to 2.98	0.001	1.32	0.80 to 2.11	0.261	1.89	1.23 to 2.87	0.003
Smoking[2] (reference = no)	1.31	1.03 to 1.67	0.031	1.47	1.12 to 1.94	0.005	2.59	2.01 to 3.38	< 0.001
Hypertension (reference = no)	1.94	1.46 to 2.59	< 0.001	2.76	1.99 to 3.87	< 0.001	2.31	1.73 to 3.10	< 0.001
Dyslipidemia (reference = no)	1.21	0.97 to 1.53	0.095	1.46	1.14 to 1.89	0.003	1.29	1.02 to 1.62	0.033
Chronic kidney disease (reference = no)	2.33	1.83 to 2.99	< 0.001	1.55	1.18 to 2.04	0.002	3.61	2.81 to 4.66	< 0.001

[1] Excluding patients with only thyroid AI disease.
[2] Either ex-smoker or current smoker.

Table 4
Multivariable logistic regression model for microvascular complications.

Covariates	Retinopathy			Neuropathy			Kidney disease[1]		
	Odds ratio	95 %CI	P-Value	Odds ratio	95 %CI	P-Value	Odds ratio	95 %CI	P-Value
No autoimmune disease (reference)	–	–		–	–		–	–	
Only thyroid AI disease	0.95	0.82 to 1.10	0.485	1.02	0.81 to 1.26	0.882	0.68	0.54 to 0.85	0.001
Other AID[2]	0.98	0.84 to 1.15	0.828	1.09	0.87 to 1.35	0.468	1.04	0.83 to 1.31	0.734
Sex (reference = male)	0.84	0.76 to 0.92	< 0.001	0.89	0.77 to 1.02	0.099	0.99	0.86 to 1.14	0.921
Age (years)	1.03	1.02 to 1.03	< 0.001	1.04	1.03 to 1.04	< 0.001	1.03	1.03 to 1.04	< 0.001
Diabetes duration (reference ≤ 10 years)	–	–		–	–		–		
Diabetes duration: 11 – 20 years	1.99	1.79 to 2.22	< 0.001	1.25	1.06 to 1.46	0.007	0.91	0.78 to 1.06	0.204
Diabetes duration: 21 – 30 years	3.29	2.83 to 3.81	< 0.001	1.66	1.32 to 2.07	< 0.001	0.96	0.76 to 1.21	0.749
Diabetes duration: 31 – 40 years	4.63	3.85 to 5.57	< 0.001	1.91	1.46 to 2.47	< 0.001	0.95	0.71 to 1.26	0.726
Diabetes duration: ≥41 years	5.90	4.70 to 7.43	< 0.001	2.76	2.11 to 3.59	< 0.001	0.99	0.72 to 1.37	0.960
Smoker[3] (reference = no)	1.26	1.17 to 1.41	< 0.001	1.43	1.24 to 1.64	< 0.001	1.37	1.19 to 1.58	< 0.001
Hypertension (reference = no)	2.18	1.96 to 2.43	< 0.001	1.89	1.62 to 2.21	< 0.001	4.51	3.88 to 5.26	< 0.001
Dyslipidemia (reference = no)	1.35	1.22 to 1.49	< 0.001	1.33	1.15 to 1.53	< 0.001	1.20	1.04 to 1.39	0.012

[1] Includes albuminuria and/or impaired renal function and/or registered diagnosis of Type 1 diabetes with renal complications (E10.2).
[2] Excluding patients with only thyroid AI disease.
[3] Either ex-smoker or current smoker.

4. Discussion

The main finding of this cross-sectional study in a large sample of subjects with T1D from a Mediterranean area is that the burden of diabetes-related complications differs according to the presence of additional AIDs. Specifically, the presence of isolated autoimmune thyroid disease is associated with a lower prevalence of kidney disease and peripheral artery disease, whereas the presence of other AIDs is associated with a higher prevalence of ischemic heart disease.

The prevalence of additional AIDs in this study is lower, especially for thyroid diseases, compared to other studies from Finland [5] or USA [3,4] with prevalences around 25%, but higher than the one described in a recent study from Germany [17] that reported a prevalence of thyroid disease of 5.7% in younger T1D patients. Differences in prevalence may be related to the age of the study population, as in most studies the prevalence of additional AIDs, specifically hypothyroidism, increases with age [4,5] and the age of diagnosis of T1D [5,26]. However, the age characteristics do not justify these differences since current age in our population is in between other reports with a higher prevalence of AIDs [4,5] and the age at diagnosis is consistently higher than in other studies [3,4,5]. In addition, the proportion of women, especially prone to AID, in our cohort is lower than in other studies [3,14,26] but similar to others [5]; our findings are also consistent with the incidence rates of T1D according to sex in Catalonia [27]. Differences found may also be attributed to regional differences of AIDs' prevalence [17,28,29] due to

variations in genetic and environmental risk factors [30] which may also be different for T1D compared to other AIDs [18]. Furthermore, the heterogeneity of screening practices may have contributed to our somewhat discordant results. In patients with T1D, screening for asymptomatic or oligosymptomatic autoimmune diseases such as autoimmune thyroiditis [31], celiac disease and pernicious anemia [32] is generally recommended with a reasonably degree of evidence, and repeated screening procedures in asymptomatic patients have been shown to lead to a higher prevalence, at least in the case of autoimmune thyroid disorders [33]. However, the lack of solid evidence on the benefit of these strategies [32] may deter healthcare providers from implementing these recommendations thus leading to underdiagnosis of these conditions.

The distribution of additional AIDs in the present study is similar to that in other studies in which thyroid diseases are the most prevalent AIDs. However, we found a higher prevalence of skin disorders, especially psoriasis, not described in other studies [4,13]. It should be noted that the reported prevalence of psoriasis is Catalonia is lower [34] than our findings and similar to that in northern Europe or USA [35].

The clinical characteristics of patients with additional AIDs are similar to previous studies showing a higher prevalence in women, older patients and patients diagnosed of T1D at older ages [4,5,26]. It has been hypothesized that the coexistence of different autoimmune disease may deteriorate glucose control at least in children and adolescents [36]. In our population, however, we did not observe a clinical relevant

difference in terms of glucose control as assessed by HbA1c values over the study period, a finding in line with other studies [5].

Data on the prevalence of diabetes-related complications in large populations with T1D and concomitant AIDs is limited [14,17]. Prinz et al. [17], in accordance with our results, have shown in a recent report a lower prevalence of microalbuminuria in young patients with T1D and Hashimoto's thyroiditis or Graves' disease. In contrast, in a smaller study in 332 European Caucasian adult patients, Rogowicz-Frontczak et al [16] found a higher prevalence of diabetes kidney disease and retinopathy in patients with T1D and Hashimoto's thyroiditis with no effect of thyroxine treatment. Some studies point to a deleterious effect of hypothyroidism on the development of diabetic nephropathy at least in patients with type 2 diabetes [37] which could be reversed by treatment with levothyroxine [38]. Unfortunately, data on TSH or thyroxine treatment were not available in our study and we cannot speculate further on this topic. We also found in T1D patients with isolated thyroid disease a lower prevalence of peripheral artery disease even after adjusting for kidney disease of which we are not aware in the literature.

In contrast to patients with isolated thyroid disease, in patients with T1D and other AIDs, we found a higher prevalence of ischemic heart disease independent of other well-known risk factors, also significant, such as age, sex, diabetes duration, smoking, hypertension and chronic kidney disease. This finding is in line with a previous study [14] showing an association of concomitant AIDs (including thyroid disease) with myocardial infarction. In their study Rogers et al. [14] found associations with ischemic stroke and kidney disease which were not observed in our population. Our results differ from those found in the Canadian Study of Longevity in Type 1 Diabetes where in longstanding type 1 diabetes, the probability of cardiovascular disease was lower in patients with autoimmune diseases driven mostly by non-thyroid diseases [15]. The presence of a higher burden of cardiovascular diseases in patients with T1D and additional AIDs seems plausible. Different studies have reported an increased risk of cardiovascular disease in autoimmune disorders [13], probably related to chronic inflammation [39].

4.1. Limitations

The present study has some limitations. As we relied on registered codes without external validation measures, we cannot exclude the possibility of underreporting of diabetes complications or autoimmune diseases, especially those not associated with specific treatments such as chronic autoimmune thyroiditis or celiac disease. These are common limitations of current primary-care-based electronic record databases highlighting the need for additional validation studies using external databases, the development of internal control algorithms, and the comparison of the results to other similar studies. In addition, we cannot exclude a misdiagnosis of other forms of diabetes (specifically pancreatic diabetes which is usually treated with insulin only) as type 1 diabetes, which would decrease the proportion of patients with susceptibility to develop other autoimmune conditions. Also, we were unable to identify patients with latent autoimmune diabetes (LADA) since ICD10 codes do not differentiate this form of diabetes. Patients with LADA should presumably be classified as T1D but misclassification is frequent, and their burden of diabetes-related complications and concomitant AIDs may be different from that of conventional T1D [40].

The proportion of missing data for laboratory parameters is also a significant limitation. This fact may be due to the fact that T1D patients are mainly managed at hospital level, with a relevant proportion of health care providers other than ICS, while only ICS hospitals transfer automatically laboratory data to the SIDIAP database. Moreover, there is also a possibility that a clinical or laboratory assessment was not performed during the study year. In addition, due to the cross-sectional design of the study, the selection bias (due to the exclusion of the deceased patients presumably with more complications), and the temporality bias limit the evaluation of the relationship between AID and diabetes-related complications. Besides these limitations, our study includes a large population of subjects which makes its findings relevant.

In summary, in this Mediterranean population of patients with T1D the presence of concomitant autoimmune thyroid diseases is associated with a lower prevalence of kidney disease and peripheral artery disease while the presence of other AIDs is associated with the presence of ischemic heart disease. These results may have implications regarding the need for early detection of AIDs and for a more aggressive treatment of cardiovascular risk factors in the presence of certain AIDs in patients with T1D. Additional cohort studies are needed to establish prediction models on morbidity and mortality according to the presence of additional AID in patients with type 1 diabetes.

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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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.110031.

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