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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, *etc.*.

INDEXING/ABSTRACTING

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ORIGINAL ARTICLE

Observational Study

Type 1 diabetes and associated autoimmune diseases

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Abstract

BACKGROUND

Common autoimmune diseases (AID) tend to occur together in the same individual and families. Type 1 diabetes (T1D) is caused by an autoimmune-induced inflammatory destruction of the pancreatic tissue and clusters with several other AID.

AIM

To compare the demographic, clinical, and serological features of patients with single T1D *vs* those with T1D and associated AID.

METHODS

From October 1999 to February 2020, a total of 665 patients with T1D and their first-degree relatives were evaluated.

RESULTS

Compared to patients with isolated T1D, those with T1D + AID were older and had a higher female: male ratio. Average patient age and age at disease onset were higher in T1D + AID *vs* T1D only. The average time interval between T1D onset and the onset of a second glandular AID was markedly shorter than the time interval between T1D and the occurrence of a non-endocrine AID. T1D-specific autoantibodies were more frequent in patients with T1D + AID and relatives *vs* those with T1D only. However, the prevalence of AID and autoantibodies against various tissues were found to be higher in relatives of patients with T1D only compared to relatives of patients with T1D + AID.

CONCLUSION

Annual serological and subsequent functional screening for AID in patients with T1D and their first-degree relatives is recommended.

Key Words: Type 1 diabetes; Autoimmunity; Serology; Antibodies; Autoimmune endocrine diseases; Autoimmune non-endocrine disorders

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Core Tip: Type 1 diabetes (T1D) often occurs in combination with several other endocrine and non-endocrine autoimmune disorders. Recent studies have revealed a strong clustering of T1D + autoimmune diseases in patients and their first-degree relatives. Therefore, regular screening for autoantibodies in patients with T1D and first-degree relatives is of upmost importance for diagnostic and therapeutic procedures of endocrine and non-endocrine autoimmunity.

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INTRODUCTION

The prevalence of type 1 diabetes (T1D) in the general population is increasing worldwide and has nearly doubled in the past 40 years in the adult population. T1D amounts to 5% to 10% of all newly diagnosed patients with diabetes mellitus, around 400 million subjects worldwide[1-5]. The incidence of T1D throughout the world is 15 *per* 100000, while its prevalence is 9.5 *per* 10000 people[6]. The global prevalence ranges from 3.5 *per* 10000 in Africa to 12.2 *per* 10000 in the United States, with 6.9 *per* 10000 in Asia and Europe, respectively[6]. The worldwide incidence of T1D ranges between 8 *per* 100000 in Africa to 20 *per* 100 in the United States, with a prevalence of 15 *per* 100000 in Asia and Europe, respectively. During the years 1989-2008, a continuous rise in the incidence of T1D in Europe of approximately 3%-4% *per* year was observed[6,7]. The multifactorial pathogenesis of T1D involves β-cell antibodies (Ab) leading to the autoimmune destruction of insulin-producing β-cells (Figure 1)[8].

Biomarkers of beta cell autoimmunity in T1D are islet cell autoantibody (ICA), insulin autoantibody (IAA), glutamic acid decarboxylase (GAD) Ab, and protein tyrosine phosphatase Ab (IA-2A)[9-11] (Table 1). The early occurrence of Ab is associated with a greater risk for T1D. Ab may appear months or even years prior to the clinical manifestation and symptoms[12-15]. In young children, with a peak under the age of five years, the first Ab to appear is IAA. A valid titer can only be measured before initiation of insulin therapy[14,16]. IAA is the first marker of T1D risk in young children and is present in approximately 70% at diagnosis. The age of diabetes onset therefore strongly and inversely correlates with the prevalence of IAA[9]. IA-2A is present in 60% of cases at T1D onset, while the presence of ICA ranges from 69% to 90% at T1D onset[9]. While titers of ICA and IAA decline after the onset of T1D, GAD-Ab positivity persists for years in T1D patients[17,18]. GAD-Ab is found in 70%-80% at first presentation. Therefore, in adults with late onset diabetes mellitus, measurement of GAD is preferred[9].

T1D manifests separately as a monoglandular autoimmunity, but also appears collectively with a variety of other non-glandular and glandular autoimmune diseases (AID)[5,8,19-22]. The association of glandular and non-glandular AID in patients with T1D has been frequently described[4,23-31]. Associated AID include autoimmune thyroid diseases (AITD, 15%-30%), type A gastritis (15%), celiac disease (3%-12%), vitiligo (1%-7%), rheumatoid arthritis (1.2%), systemic lupus erythematosus (1.15%), and Addison disease (AD) (0.5%)[29,32-40]. In all associated AID, auto-Ab against specific antigens lead to inflammatory reactions and often subsequent tissue destruction (Table 2). In the present longitudinal, long-term observational study performed at a referral academic center for autoimmune endocrine diseases, we aimed to compare the demographic, clinical and serological data of patients with single T1D and their relatives *vs* those with T1D and associated AID.

MATERIALS AND METHODS

In accordance with the Declaration of Helsinki, patient data were not passed to third

Table 1 Relevant autoantibodies in type 1 diabetes[10,11,72-75,77,78]

Autoantibody against	Antigen	Sensitivity (%)	Specificity (%)	Normal range	Occurrence
Glutamic acid decarboxylase	Glutamic acid decarboxylase (65 kd)	65-75	99	< 10 IE/mL	70% more common after adolescence
Islet cell	Islet cells	70	99	Negative	80% at diagnosis
Protein tyrosine phosphatase	Tyrosine phosphatase-related islet antigen 2	50-90	99	< 1.0 U/mL	60% at diagnosis
Insulin	Pro-/insulin	74	99	< 0.4 U/mL	50% at diagnosis. First Ab detected in children. Less common after adolescence
Zinc transporter 8	C terminal domain of the zinc transporter 8	65-75	99	< 15 U/mL	Up to 80% at diagnosis
Thyroglobulin	Thyroglobulin	90	99	< 4.1 IU/mL	10%-20% in GD and up to 50% in HT at diagnosis
Thyroperoxidase	Thyroperoxidase	90	99	< 6 IU /mL	70% in GD and 90% in HT at diagnosis
TSH-receptor	TSH-receptor	99	99	< 1.8 IU/mL	More than 90% in GD and 10% in HT at diagnosis
Adrenal cortex	21-hydroxylase and 17 alpha hydroxylase	87	99	Negative	Up to 90% at diagnosis of AD
Transglutaminase IgA	Tissue transglutaminase	90	99	< 20 CU	Common at diagnosis of CD. 6% of patients have an IgA deficiency
Parietal cell	Parietal cells	90	50	Negative	> 90% patients with autoimmune gastritis
Intrinsic factor	Intrinsic factor	80	90	Negative	In 50%-70% of patients with autoimmune gastritis
CCP	CCP	20-25	95	< 20.0 U	In 50%-90% of patients with rheumatoid arthritis
Anti-ro; anti-la	Heterogeneous nuclear ribonucleoproteins	89	99	Negative	70% of patients with Sjögren's syndrome and 50% of patients with lupus erythematosus
Smooth muscle	Smooth muscle	80	99	Negative	In 50%-85% of patients with autoimmune hepatitis
DNA	Double-stranded DNA	65	99	< 30.0 IU/mL	In 50%-70% of patients with systemic lupus erythematosus

CCP: Cyclic citrullinated peptide; GD: Graves' disease; Ab: Antibodies; HT: Hashimoto's thyroiditis; AD: Addison disease; CD: Celiac disease.

parties and this observational study did not include any interventions aside from routine examination and testing. The medical records of a total of 665 consecutively followed and unselected patients with T1D and T1D + AID, as well as their first-degree relatives were analyzed. All patients and their relatives were followed at the ORPHAN Center for Endocrine AID, Johannes Gutenberg University (JGU) Medical Center, between October 1999 and February 2020.

All patients and relatives were screened for symptoms and signs of suspected AID. Diseases were diagnosed and characterized according to an interview regarding their medical history, agreed-upon definition, typical clinical presentation and specific serology. The reference ranges of the JGU Central Laboratory were set as cut-offs. For data acquisition standardized clinical and laboratory diagnostic criteria were used. Only patients with confirmed T1D were included in the analysis. Diagnosis of recent-onset T1D was based on patient history, typical symptoms and most importantly measurement of organ-specific Ab. Diagnosis of AITD was based on thyroid Ab levels, thyroid sonography and clinical features[41-45]. AITD, a complex group of disorders with diverse clinical manifestations including hyperthyroidism, hypothyroidism, and goiter, are commonly detected by specific biomarkers[46]. Autoantibodies against the thyrotropin receptor (TSHR-Ab) induce the typical clinical phenotype of AITD[47-49]. Graves' disease (GD) was defined as enhanced vascularization on thyroid ultrasound, positive TSHR-Ab, a suppressed baseline TSH and elevated free thyroid hormones, such as free triiodothyronine (FT3) and/or free thyroxine (FT4)[50]. Hashimoto's thyroiditis (HT) was defined as a hypoechoic appearance on thyroid ultrasound, an elevated serum level of anti-thyroid peroxidase-Ab, with or without increased serum concentration of anti-thyroglobulin-Ab and euthyroidism or hypothyroidism[51]. TSHR-

Table 2 Autoimmune diseases with corresponding autoantigens and tissue

AID	Tissue	Antigen
Hashimoto's thyroiditis	Thyroid enzyme/protein	Thyroid peroxidase/thyroglobulin
Graves' disease	Thyrocytes	TSH receptor
Hypogonadism	Gonads, Leydig-/theca cells	17-hydroxylase, cytochrome-P450 side-chain cleavage
Addison disease	Adrenal cortex enzyme	21-hydroxylase, cytochrome-P450 side-chain cleavage
Hypoparathyroidism	Parathyroid	Ca^{2+} sensitive receptor
Type A gastritis	Parietal cells	H^+, K^+-ATPase
Vitiligo	Melanocytes	Tyrosinase
Celiac disease	Small intestine	Transglutaminase, gliadin
Neurodermatitis	Skin	IgE receptor
Psoriasis	Skin	Keratin
Alopecia	Hair follicles	Tyrosine hydroxylase
Urticaria	Skin	IgE receptor FcERI, immunoglobulin E
Sjögren's Syndrome	Salivary glands	SS-A/Ro and SS-B/La
Rheumatoid arthritis	Synovial membrane	CCP
Autoimmune hepatitis	Liver cells	Smooth muscle, liver-kidney-microsome, soluble liver antigen, liver-pancreas antigen
Systemic lupus erythematosus	Skin, vascular connective tissue	Double-stranded DNA
Crohn's disease	Gastrointestinal tract	Microbial antigens

AID: Autoimmune diseases; TSH: Thyrotropin or thyroid stimulating hormone; CCP: Cyclic citrullinated peptide.

Ab are either acting as an agonist and stimulate unregulated thyroid growth as well as thyroid hormone production, or as an antagonist, blocking the activity of the natural ligand thyrotropin[45,52-55]. TSHR-stimulating Ab (TSAb), activating the TSHR causing an unregulated stimulation of thyroid cells, lead to GD[56]. Functional TSHR-blocking autoantibodies (TBAb) induce primary autoimmune hypothyroidism and occur in patients with HT[49,57,58]. The co-occurrence of both TSAb and TBAb in the same patient might explain the spectrum of clinical presentations. Diagnosis criteria for AD[59] were positive cytochrome P450-21 hydroxylase Ab, suppressed baseline serum cortisol levels, elevated adrenocorticotrophic hormone (ACTH) levels together with elevated stimulated serum ACTH levels. Autoimmune primary hypoparathyroidism[30,60] was diagnosed through serum baseline parathyroid hormone levels, baseline serum calcium, and elevated serum phosphate levels and the presence of anti-calcium-sensing receptor Ab.

Autoimmune primary hypogonadism was diagnosed by positive 17-hydroxylase Ab, increased gonadotrophic hormone levels, as well as decreased peripheral sexual hormone levels. Celiac disease (CD) was defined as a life-long intolerance to dietary gluten, resulting in small intestinal inflammation. The ingestion of gluten mainly contained in wheat, rye, and barley, leads to a T cell driven auto-destructive process within the small intestinal mucosa. Tissue transglutaminase, a multifunctional enzyme, changes the amino acid glutamine into glutamate, through deamination. Glutamate leads to more CD4+ T cells activation resulting in an enhanced immunogenicity[61]. The presence of CD in patients with T1D is often indicated by frequent episodes of hypoglycemia, a reduction of insulin requirements and brittle diabetes. Some common pathogenic mechanisms, such as increased intestinal permeability resulting from zonulin upregulation and dysfunction of tight junctions have been implicated, in both CD and T1D[29,62-64].

Autoimmune type A gastritis was diagnosed by the presence of gastric parietal cell-Ab in the serum with intestinal metaplasia and atrophy of the gastric mucosa. Diagnostic criteria for rheumatoid arthritis were typical symptoms and signs, as well as laboratory tests including positive rheumatoid factor and cyclic citrullinated peptide. Autoimmune hepatitis was diagnosed by elevated anti-soluble liver antigen Ab or anti-alpha smooth muscle actin, in the presence of at least two-fold elevated aspartate aminotransferase or alanine aminotransferase values.

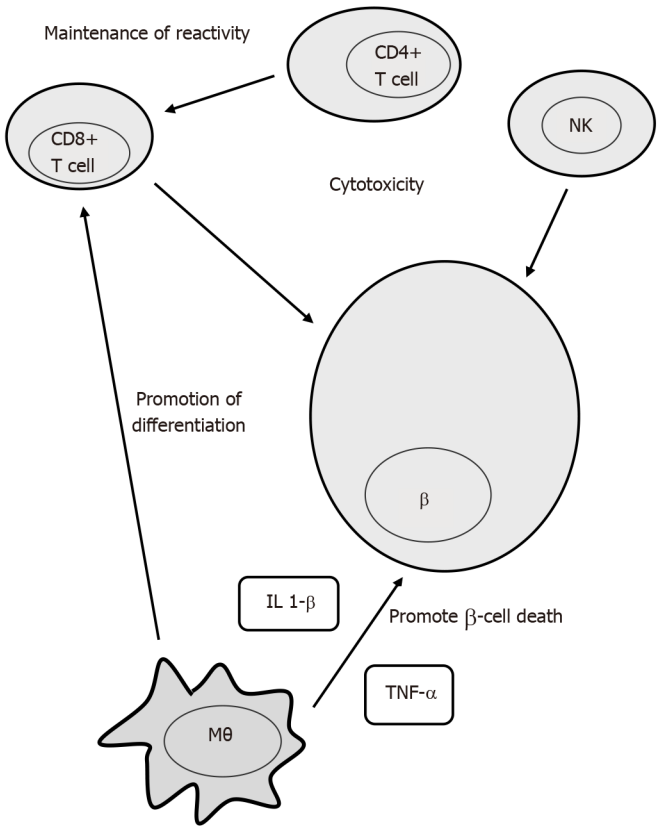

Figure 1 Pathogenesis of type 1 diabetes-cellular crosstalk. CD: Celiac disease; TNF-α: Tumor necrosis factor-α; IL 1-β: Interleukin 1-β; NK: Natural killer cell.

Sjögren's syndrome was diagnosed by positive anti-SS-A-Ab and SS-B-Ab and a positive salivary gland biopsy. Systemic lupus erythematosus was diagnosed by the presence of double-stranded DNA-Ab together with a classical phenotype. Diagnostic criteria for myasthenia gravis were serum acetylcholine receptor Ab. Further information on AID with corresponding tissues and antigens as diagnostic criteria are listed in Table 2.

RESULTS

Demographic data

Compared to patients with T1D only, the female to male ratio was approximately two-fold greater in patients with T1D + AID. Furthermore, the mean age of patients with T1D only was markedly lower in comparison to the combination group. Mean age at T1D onset was significantly higher in the combination group (Table 3). At T1D onset, the oldest patient was significantly older in the combined disease group *vs* T1D only. Average disease duration of T1D was similar in both groups. More importantly, the average time interval between T1D onset and the onset of a second glandular AID was markedly shorter (13 ± 12 years) than the time interval between T1D and the occurrence of a non-endocrine AID (19 ± 15 years).

On average, we observed two and a maximum of five associated AID. More patients with AID were followed than patients with T1D only; hence, nearly two-fold more relatives of patients with T1D + AID were included. Slightly more T1D relatives were also affected by AID (58.1%) when compared to the T1D + AID (44.3%) relatives.

Clinical and serological data of patients

As shown in Figure 2, the most frequent endocrine and non–endocrine AID in patients with T1D were HT, GD, type A gastritis, vitiligo, neurodermatitis, and CD, respectively[4].

Table 3 Demographic data

Disease	T1D	T1D + AID
n	131	211
Sex (male/female)	64/67	70/141
Mean age (yr, SD)	33 (± 16)	56 (± 16)
Ethnicity	Caucasian	Caucasian
Mean age at onset (yr, SD)	19 (± 12)	29 (± 18)
Youngest onset (yr)	1	1
Oldest onset (yr)	55	77
Mean duration of T1D (yr, SD)	28 (± 14)	27 (± 16)
Relatives (*n*)	68	255

T1D: Type 1 diabetes; AID: Autoimmune diseases; Yr.: Year; SD: Standard deviation.

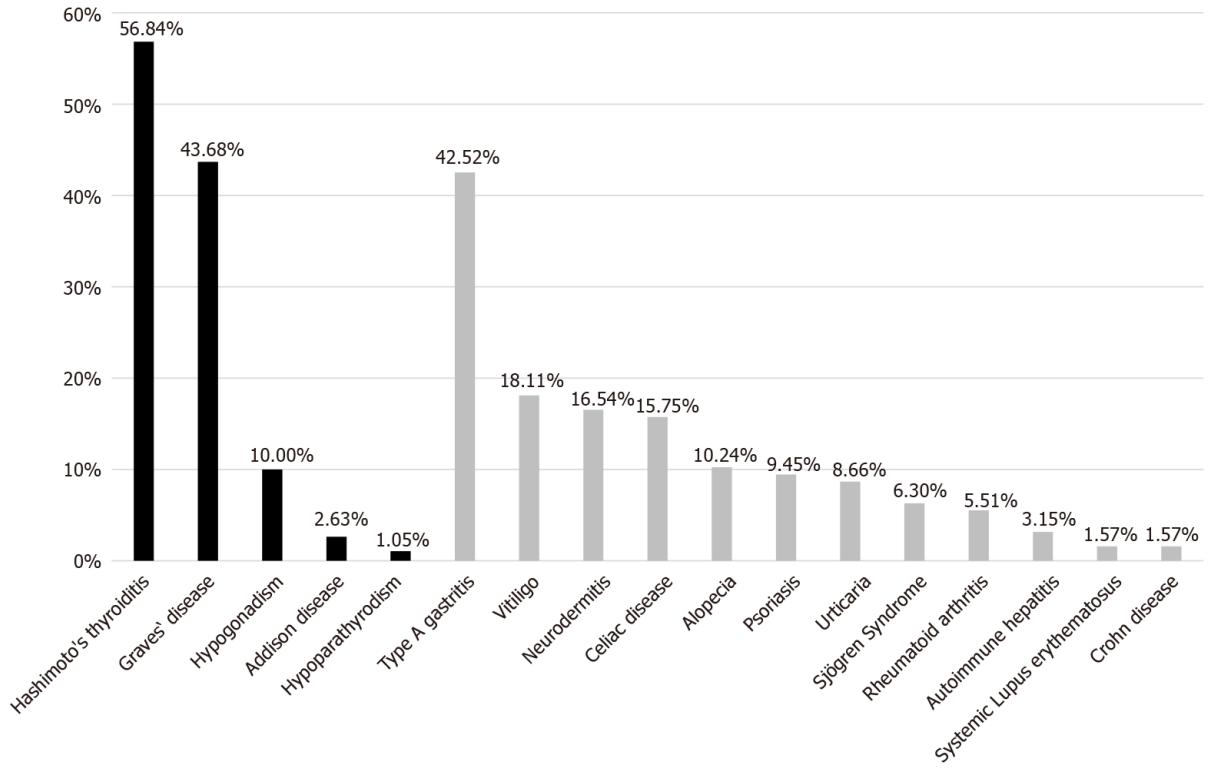

Figure 2 Associated autoimmune disorders in type 1 diabetes. The prevalence of associated glandular (black) and non-glandular (light grey) autoimmune diseases in patients with type 1 diabetes + autoimmune diseases, followed at the Johannes Gutenberg University Medical Center.

Figure 3 demonstrates the Ab profile in patients with T1D only and the various positive Ab findings in those with T1D + AID. The prevalence of Ab against various other tissues was found to be higher in patients with T1D + AID. GAD-Ab positivity was more frequent in the patients with combined T1D + AID. All T1D + AID patients with positive thyroid Ab had thyroid dysfunction. Furthermore, of the patients with previously diagnosed CD, only 36% were further positive for Transglutaminase IgA. Of the patients with positive parietal cell Ab and/or intrinsic factor Ab, 88% had a positive biopsy result for destruction of the gastric gland with neuroendocrine metaplasia of the gastric mucosa.

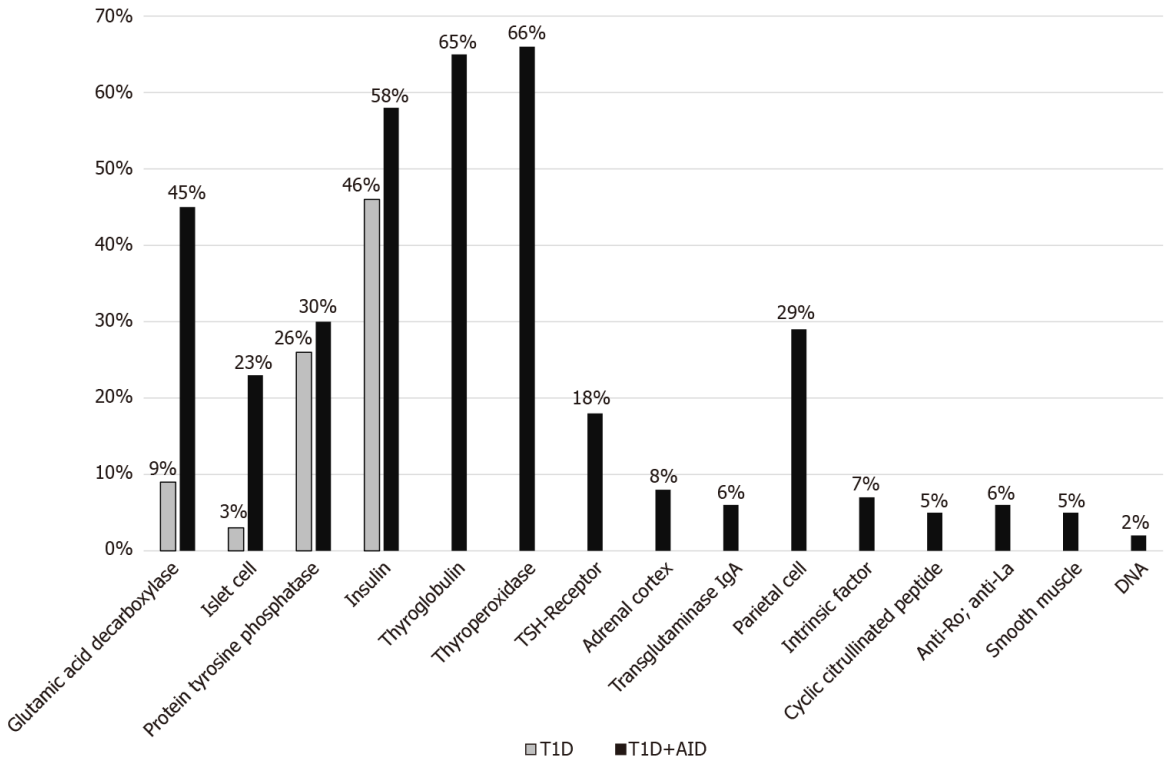

Figure 3 Prevalence of autoantibodies in type 1 diabetes. The prevalence of autoantibodies in patients with type 1 diabetes (T1D) (light grey) and in patients with T1D + autoimmune diseases (black), followed at the Johannes Gutenberg University Medical Center. T1D: Type 1 diabetes; AID: Autoimmune diseases.

Clinical and serological data of relatives

IAA was the most frequent diabetes Ab in relatives of both patients with T1D only and in those with AID + T1D. Of relatives with positive IAA, 25% were diagnosed with other AID, but not T1D, and 35% were not diagnosed with AID. In contrast, IA2-Ab was the least prevalent Ab. However, this Ab was always associated with the diagnosis of T1D in the IA2 (+) relatives. Hence, all relatives with positive IA2-Ab were diagnosed with T1D. The second most frequent positive Ab was IA2A in patients with T1D only and GAD-Ab in patients with T1D + AID. In the relatives of patients with T1D, nearly all subjects with positive diabetes Ab titers had diagnosed T1D (> 90%), and in the relatives of patients with T1D + AID, approximately 35% of Ab-positive subjects had no AID. The prevalence of Ab against various other tissues was found to be higher in relatives of patients with isolated T1D (Figure 4).

All relatives of patients with isolated T1D and positive thyroid Ab had thyroid dysfunction. Also, all relatives with positive Transglutaminase A Ab were diagnosed with CD. Finally, all relatives with positive parietal cell Ab and/or intrinsic factor Ab had a positive macroscopic and histological finding of type A autoimmune gastritis.

In comparison, only 72% of T1D + AID relatives with at least one positive thyroid Ab had thyroid dysfunction. The same was true for 54% of T1D + AID relatives with positive parietal cell Ab and/or intrinsic factor Ab and endoscopy confirmed type A gastritis. In contrast, all relatives with positive Transglutaminase A Ab had confirmed macroscopic and histologically confirmed CD.

DISCUSSION

This longitudinal long-term observational study of a large collective of unselected and consecutively followed patients with T1D at an academic referral center for endocrine AID has shown several relevant findings. First, as expected T1D often clusters with several other AID. Gastrointestinal AID such as type A gastritis and CD are often prevalent in patients with T1D + AID, while HT is the most frequent AITD. Therefore, at the manifestation of T1D, whether as a monoglandular disease or in combination with another AID, serological and subsequent functional screening for additional

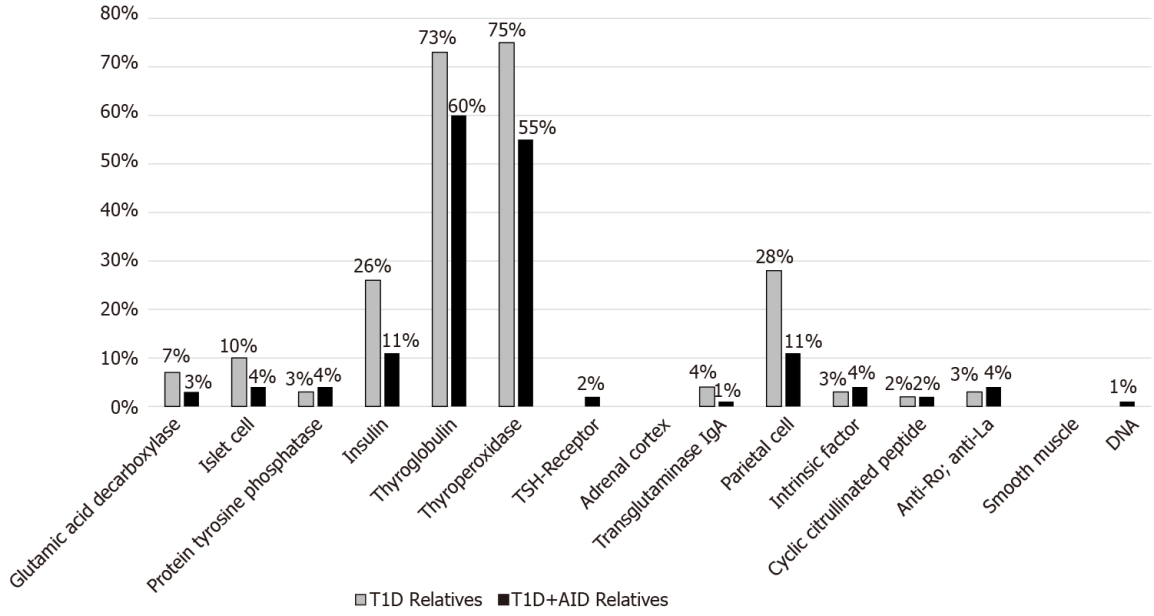

Figure 4 Autoantibodies in relatives. Prevalence of autoantibodies in the relatives of patients with type 1 diabetes only (T1D) (light grey) and in the relatives of those with T1D + autoimmune diseases (AID, black). T1D: Type 1 diabetes; AID: Autoimmune diseases.

glandular and non-glandular AID are recommended[65,66].

Secondly, in this study the demographic data of patients with isolated T1D *vs* those in the combined group differed significantly, showing a different sex and age profile. In general, the first onset of T1D mostly occurs between ages 8 to 14 years close to puberty, while the gender ratio shows a slight preponderance of males. The highest incidence of T1D is at ages 5 to 9 years and 10 to 14 in girls and boys, respectively[7,67,68]. Our results may be explained by the fact that the combination group of T1D + AID included patients with AITD, such as HT and GD and these AID occur significantly more often in females[3,5,28,69,70]. Furthermore, compared to T1D only, the "combination" group was older with a later disease onset. AITD most commonly peaks in the fourth decade in patients with GD or in the fifth to sixth decade in those with HT[28,71], and in combination with AID, disease onset of T1D seems to be delayed compared to isolated T1D.

Thirdly, serological data differed in both groups. IAA was the Ab most frequently found to be positive in both groups. Thus, this Ab was detected at T1D onset and prior to treatment. Indeed, IAA was the first Ab in T1D to appear, and subsequently declined with time and during specific insulin treatment[10,11,72,73]. GAD-Ab are more commonly found in subjects diagnosed after adolescence, are present in patients at clinical presentation of T1D, especially with latent autoimmune diabetes in adults, and remain positive long after diagnosis and during disease treatment[10,11,73]. In comparison, ICA was the Ab least often measured as positive in both groups, as it is declines quickly with time and during the course of treatment[10,11,74,75]. In patients with T1D + AID, positivity rates are higher for all Ab. Most of the Ab decline with time and treatment after disease onset. Because the average age of disease onset is later in patients with T1D + AID, on average not much time since onset of disease might have passed when Ab were measured. Also, these patients are screened more often for Ab, since the risk of developing more AID increases with the number of glandular and non-glandular disorders present and T1D might has been detected early in these patients. Approximately one third of T1D patients will develop thyroid-Ab and thyroid dysfunction[3]. Since endocrine AID associated with T1D strongly impacts patients' treatment with insulin, screening for adrenal 21-hydroxylase-Ab should be considered in all patients with T1D, while screening of GAD-Ab in all patients with AD is recommended[3]. The management of T1D associated with other AID requires care by specialized centers for endocrine and metabolic AID. Therefore, general organ-specific Ab screening and functional testing in patients with either monoglandular T1D or monoglandular AD will help identify subjects at risk for developing polyglandular autoimmunity[28,76].

Fourthly, relatives of patients with combined T1D + AID are more often affected by

glandular or non-glandular AID. In both groups, HT is the most frequent AID, but relatives of patients with only T1D are more often themselves affected by T1D and in both relatives of patients with isolated T1D as well as with T1D + AID, positive Ab titers are found[77]. Many of these relatives with positive Ab were not diagnosed with T1D; some had no diagnosed AID at all. As in patients, gastrointestinal AID such as type A gastritis and CD are often prevalent in relatives, too. Based on the genetic component in endocrine AID, the risk of developing T1D or an associated AID is significantly elevated in first-degree relatives of patients with T1D or in families of patients with T1D + AID. Therefore, an important tool for the early detection of AID in first-degree relatives is regular serological screening.

In this study, we investigated a large cohort of unselected consecutive patients with T1D seen at a specialized academic referral outpatient clinic for endocrine AID. Patients with multiple AID, especially multiple endocrine AID are usually referred to a specialized center due to the severity of their disease phenotype. This might have led to the inclusion of more patients with several AID thus creating a selection bias. Another limitation is the possibility of a misclassification of "isolated T1D" in the present study, as asymptomatic AID without clinical presentation might have been present but not yet detected.

CONCLUSION

In conclusion, based on our large database and longitudinally collected long-term data, we recommend regular investigations of each patient with T1D for symptoms and markers of further glandular and non-endocrine AID. Serological screening of first-degree relatives of T1D patients is also recommended.

ARTICLE HIGHLIGHTS

Research background

Autoimmune diseases (AID) tend to occur together in the same subjects and cluster in families. Type 1 diabetes (T1D) is caused by an autoimmune-induced inflammatory destruction of the pancreatic tissue and clusters with several other AID.

Research motivation

To obtain a better understanding of the clustering of several autoimmune diseases in the same subject and related families.

Research objectives

With this longitudinal, long-term observational study, we aimed to compare the demographic, clinical, and serological features of patients with single T1D *vs* those with T1D and associated AID and to analyze the frequency of other AID in T1D.

Research methods

From October 1999 to February 2020, the medical records of a total of 665 patients with T1D and their first-degree relatives were evaluated. All patients and relatives were screened for signs and symptoms of suspected AID. Diseases were diagnosed and characterized according to an interview regarding their medical history, agreed-upon definition, typical clinical presentation and specific serology. The Johannes Gutenberg University Central Laboratory reference ranges were set as cut-offs, while for data acquisition, standardized clinical and laboratory diagnostic criteria were used. Only patients with confirmed T1D were included in the analysis.

Research results

A total of 665 patients with T1D and their first-degree relatives were evaluated. Compared to patients with T1D only, the female to male ratio was approximately two-fold greater in patients with T1D + AID. The mean age of patients with T1D was 33 (± 16) years and 56 (± 16) years for patients with T1D + AID. Average disease duration of T1D was similar in both groups. More importantly, the average time interval between T1D onset and the onset of a second glandular AID was markedly shorter (13 ± 12 years) than the time interval between T1D and the occurrence of a non-endocrine AID (19 ± 15 years).

On average, we observed two associated AID, with a minimum of zero and a maximum of five. We found slightly more T1D relatives were also affected by AID (58.1%) when compared to T1D + AID (44.3%) relatives. The prevalence of autoantibodies (Ab) against various other tissues was found to be higher in patients with T1D + AID. In the relatives of patients with T1D, nearly all subjects with positive diabetes Ab titers had diagnosed T1D (> 90%), and in the relatives of patients with T1D + AID, approximately 35% of Ab-positive subjects had no AID. The prevalence of Ab against various other tissues was found to be higher in relatives of patients with isolated T1D.

Research conclusions

As expected we found that T1D often clusters with several other AID. Gastrointestinal AID such as type A gastritis and celiac disease are often prevalent in patients with T1D + AID, while Hashimoto's thyroiditis (HT) is the most frequent autoimmune thyroid disease (AITD). Therefore, at the onset of T1D, whether as a monoglandular disease or in combination with another AID, serological and subsequent functional screening for additional glandular and non-glandular AID are recommended. The significantly different sex profile in patients with isolated T1D *vs* those in the combined group may be explained by the fact that AITD, such as HT and Graves' disease occur significantly more often in females. High Ab titers in the combination group (T1D + AID) might be explained by the later disease onset of diabetes in patients with T1D + AID. On average not as much time since onset of disease might have passed when Ab were measured.

Research perspectives

In this study, we compared patients with isolated T1D to patients with T1D + AID. We found that approximately one third of T1D patients will develop thyroid-Ab and thyroid dysfunction; therefore, general organ-specific Ab screening and functional testing in patients with either monoglandular T1D or monoglandular Addison disease, will help identify subjects at risk of developing polyglandular autoimmunity, and management of T1D associated with other AID requires care by specialized centers for endocrine and metabolic AID. We also recommend serological screening of first-degree relatives of T1D patients.

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