Autoimmune diseases and their prevalence in Saudi Arabian patients with type 1 diabetes mellitus

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ABSTRACT

الأهداف: لتقييم انتشار اضطرابات المناعة الذاتية بين الشباب والبالغين المصابين بداء السكري من النوع الأول (T1DM) في المدينة المنورة، المملكة العربية السعودية، ولتقييم التأثير المحتمل لهذه الحالات على الأمراض المصاحبة الأخرى.

المنهجية: دراسة وصفية بأثر رجعي بحثت في أمراض المناعة الذاتية لدى الشباب والبالغين المصابين بـ T1DM. تم فحص إجمالي 2258 مريض مؤكد اصابته بـ T1DM. تم تحليل بيانات المختبر والمستشفى. تم فحص الخصائص السريرية والجزيئية لـ T1DM مع أمراض المناعة الذاتية.

النتائج: تمت دراسة ما مجموعه 2258 T1DM من البالغين والمراهقين والأطفال. كان إجمالي 500 (22.2٪) تحت سن 12، و 540 (23.9٪) كانوا 13–17، و 1218 (53.9٪) كانوا فوق 18 سنة. ما يقرب من 67.4٪ لديهم T1DM مع أمراض المناعة الذاتية. تفاوت معدل الانتشار حسب الجنس والعمر. ما يقرب 25.7٪ من الإناث البالغات يعانين من حالات التهاب الغدة الدرقية المناعي الذاتي. كان مرض الاضطرابات الهضمية أكثر شيوعًا لدى الأطفال والمراهقين منه لدى البالغين من كلا الجنسين. كان البالغون أكثر عُرضة للإصابة بقصور الغدة الكظرية من الأطفال والمراهقين. أثرت اضطرابات المناعة الذاتية متعددة الغدد على 28.5٪ من الرجال البالغين و 19.7٪ من النساء. يُظهر الأفراد المصابون بـ T1DM واضطرابات المناعة الذاتية الأخرى ارتفاعًا في حالات اعتلال الكلى وأمراض القلب والأوعية الدموية (CVD) ونقص السكر في الدم مقارنةً بالحالات الأخرى. يتم دعم ذلك من خلال وجود المؤشرات الحيوية في مجرى الدم المرتبطة بالمضاعفات المذكورة أعلاه.

الخلاصة: أظهرت أمراض المناعة الذاتية في المرضى السعوديين الذين يعانون من T1DM اختلافاً فيما يتعلق بالجنس والعمر. المدينة المنورة لديها انتشار متزايد لأمراض المناعة الذاتية بين الشباب الذين تم تشخيصهم بـ T1DM ، مثل مرض الاضطرابات الهضمية والتهاب الغدة الدرقية المناعي. على العكس من ذلك ، فقد لوحظ أن الأفراد الأكبر سنًا في المنطقة يظهرون نسبة أكبر من فشل الغدة الكظرية واضطرابات المناعة الذاتية متعددة الغدد. تنتشر أمراض المناعة الذاتية التي تؤدي إلى اعتلال الكلية والأمراض القلبية الوعائية ونقص السكر في الدم بشكل كبير بناءً على مستويات المؤشرات الحيوية.

Objectives: To evaluate the prevalence of autoimmune disorders among young and adult populations diagnosed with type 1 diabetes mellitus (T1DM) in Al-Madinah Al-Munawarah, Saudi Arabia, and assess the potential impact of these conditions on other comorbidities.

Methods: A retrospective, descriptive study examined autoimmune disorders in T1DM youth and adults. A total of 2258 verified T1DMs were tested. Analyzed hospital and laboratory data. Autoimmune T1DM was investigated clinically and laboratory.

Results: A total of 2258 T1DM adults, adolescents, and children were investigated; 500 (22.2%) were under 12, 540 (23.9%) were 13–17, and 1218 (53.9%) were 18 plus. Autoimmune with T1DM was 67.4%. Gender and age affect prevalence. 25.7% of adult females had autoimmune thyroiditis. Children and adolescents have greater rates of celiac disease than adults of both genders. Adrenal insufficiency was more frequent in adults. Adult males had 28.5% polyglandular autoimmune diseases, and women had 19.7%. Type 1 DM and other autoimmune illnesses increase the risk of nephropathy, CVD, and hypoglycemia. Bloodstream biomarkers linked to these disorders corroborate this.

Conclusion: Autoimmune diseases in Saudi patients with T1DM exhibited specificity with respect to gender and age. Al-Madinah Al-Munawwarah have a heightened prevalence of autoimmune diseases among young individuals diagnosed with T1DM, such as celiac disease and autoimmune thyroiditis. Conversely, older individuals in the region have been observed to exhibit a greater incidence of adrenal failure and polyglandular autoimmune disorders. Autoimmune diseases that result in nephropathy, CVD, and hypoglycemia are highly prevalent based on biomarker levels.

Keywords: autoimmune disease, autoimmune thyroid, celiac disease, adrenal insufficiency, polyglandular autoimmune syndromes, type 1 diabetes, Saudi Arabia

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Our immune system is incredibly sophisticated. It defends the body from malignant cells and outside threats. The immune system accidentally attacks the beta-cells that produce insulin in the pancreas in type 1 diabetes mellitus (T1DM); this can take place over a few weeks, months, or years. Because of this, it is necessary to substitute insulin with a pump or frequent injections. Without insulin, blood glucose levels continue to rise and can have disastrous consequences, including ketosis and abrupt cardiac death.[1] Based on estimations, it is reported that there are approximately 387 million individuals globally who are affected by diabetes mellitus, with 5-10% of these individuals being diagnosed with T1DM.[2,3] Based on the currently available data, it appears that the occurrence of T1DM in Saudi Arabia is approximately 109.5 cases per 100,000 individuals. Furthermore, the incidence rate of T1DM is observed to be rising at a rate of 3% annually.[4,5] A study was carried out in the United States involving 491 children diagnosed with T1DM to investigate the screening methods for autoimmune thyroid disease (AITD), celiac disease (CD), and adrenal insufficiency (AI). The prevalence of thyroid illness among the studied adolescents was found to be 12.3%, while 24.8% of them exhibited positive results for thyroid peroxidase (TPO) autoantibodies. Furthermore, the prevalence of CD was observed in 24.6% of individuals who tested positive for tissue transglutaminase autoantibodies (tTG) among the 11.6% of the study population. One of the participants, constituting 1% of the sample, who were screened for 21-hydroxylase autoantibodies, was diagnosed with Addison disease.[6] The comorbidity of T1DM with autoimmune disorders impacting the thyroid, adrenals, and gastrointestinal systems is widely acknowledged. This phenomenon has been extensively researched and analyzed in various studies.[7-10] Several inquiries were carried out in Saudi Arabia to investigate the frequency of autoimmune disorders among young patients diagnosed with T1DM. In Aseer, Saudi Arabia, 202 patients with T1DM were the subjects of a cross-sectional study. One incidence of anti-cyclic citrullinated peptide positivity was reported, while 10.4% of patients had a double positive for tissue transglutaminase IgA antibody and endomysial antibody. Of the patients, 16% had thyroid autoantibodies.[11] In a different cross-sectional study carried out in Jeddah, Saudi Arabia, on 228 children and teenagers with T1DM, 14% of the patients had autoimmune thyroiditis and 19.7% had CD.[12] In addition, investigations carried out in King Khalid University Hospital, Riyadh, Saudi Arabia, in a cohort of 305 children and adolescents examined the development of related autoimmune illnesses over a 15-year period. Approximately 8.5% of the patients had overt hypothyroidism, 8.5% had CD confirmed by intestinal biopsy results, and only one patient had AI as a component of autoimmune polyendocrine syndrome type 1.[13,14] Thyroid functions were found to be abnormal in 21.3% of the patients (8.5% had evidence of overt hypothyroidism). To assess the frequency of asymptomatic CD among T1DM patients, a recent study was carried out in Al-Baha Diabetic Center, Al Bahah Region, Southwestern Saudi Arabia. The study found that, of the 268 T1DM patients tested, the approximated serology-positive prevalence was 7.1%.[15] The pediatric age group was used for all prior research. However, one study in King Abdulaziz Medical City Diabetic Center, Riyadh, Saudi Arabia, with the aim of estimating the prevalence of autoimmune diseases associated with T1DM among the adult age group found that of the 251 T1DM patients screened, the prevalence of hypothyroidism was 16.3%, TPO positivity was found in 58.6% of diabetic patients, and 16.5% of adult subjects had CD.[16] The research aims to assess the prevalence of autoimmune diseases associated with T1DM across adult, adolescent, and pediatric age groups in Al-Madinah Al-Munawwarah, Saudi Arabia, given the lack of available local data on the subject. Moreover, the predominant focus of prior research has been limited to examining the correlation between CD and thyroid disorders. In contrast, our investigation extends beyond this scope by also investigating the association between AI and polyglandular autoimmune syndromes II (APS-II). Additionally, our objective is to assess the incidence of glycemic complications and unfavorable outcomes, such as nephropathy and cardiovascular disease (CVD), among the individuals enrolled in our study.

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Methods. This study was carried out at King Fahad Hospital, Al-Madinah Al-Munawwarah, Saudi Arabia, at the Endocrinology and Diabetes Unit. From January 2019 to December 2022, electronic records were evaluated for T1DM patients with and without autoimmune disorders. The Institutional Review Board, General Directorate of Health Affairs in Al-Madinah Al-Munawwarah provided ethical approval (approval no.# IRB22-046). This investigation, which had 2258 consecutive patients, was retrospective and descriptive. The patients were chosen from a group of

outpatient diabetic patients at the Endocrinology and Diabetes Center, King Fahad Hospital, Al-Madinah Al-Munawwarah. All patient information had been fully documented in the patient files, creating a clear database of data that could be analyzed. Age, gender, anthropometric measurements (height, weight, body mass index [BMI]), laboratory findings (fasting blood glucose [FBG], hemoglobin A1C [HbA1c] which was determined in the laboratory and verified mathematically: average blood glucose (mmol/L) = (HbA1c*1.98)-4.29),[17] lipid profiles, renal function test (creatinine), Liver function test (albumin, alkaline phosphatase [ALP]), and diagnoses were all analyzed. We retrieved and evaluated data for 2258 patients (1349 female and 909 male) who are generally diagnosed with different types of autoimmune diseases after the T1DM diagnosis. The diagnostic procedures for T1DM involve a series of blood tests, namely FBG, HbA1c, and C-peptide level below 5 μU/mL (0.6 ng/mL). Additionally, the assessment of diabetes-related autoantibodies in patients was carried out, which included the evaluation of islet cell autoantibody (ICA) and glutamic acid decarboxylase autoantibody (GADA), all of this data was extracted and evaluated from patient files. Age groups reference range included: I) children (≤12 years); II) adolescents (13-17 years); and III) adults (≥18 years).[18]

Autoimmune disorders refer to the pathological states in which the immune system erroneously attacks and harms healthy cells within the body. The aforementioned conditions are classified as T1DM, AITD, CD, AI, and APS.

Autoimmune thyroid diseases encompass a range of conditions, hypothyroidism which is primarily caused by Hashimoto's thyroiditis or hyperthyroidism is caused by Graves' disease. The physician's report relied on clinical diagnosis and the presence of positive antibodies, specifically anti-thyroperoxidase (TPO), as well as changes in thyroid-stimulating hormone (TSH) and thyroid hormones (T3 and T4). The data was extracted and evaluated from patient files. However, there was no distinction carried out between hypothyroidism and hyperthyroidism in the current study.

Celiac disease is an autoimmune disorder that is triggered by the ingestion of gluten and affects multiple systems within the body. It is distinguished by the detection of anti-tissue transglutaminase antibody. The present investigation involved the diagnosis of CD in patients, which was previously established through the physician's report on the results of blood tests (tTG autoantibodies and IgA) and endoscopy of the small intestine.

Adrenal insufficiency is categorized as an autoimmune disorder due to its etiology, which involves an aberrant immune response targeting the adrenal glands. The typical range of plasma corticotropin concentrations at 8 AM is 10-60 pg/mL (2.2-13.3 pmol/L), while cortisol concentrations typically range from 5-25 mcg/dL or 140-690 nmol/L at the same time. Another diagnostic test is adrenal 21-hydroxylase antibodies. The current investigation pertained to the identification of AI in individuals, which had been previously confirmed based on the medical practitioner's documentation of the outcomes of hematological analyses.

Polyglandular autoimmune syndromes type 2 is characterized by the co-occurrence of an autoimmune endocrine disorder and another autoimmune disease, without satisfying the criteria for APS-I and lacking a discernible gene mutation. The diagnosis of the condition was established upon the manifestation of a minimum of 2 out of 3 criteria (namely, primary AI and AITD) leading to hyperthyroidism or hypothyroidism, and T1DM.

The present study examined the various complications experienced by patients diagnosed with T1DM, utilizing their medical records and reports provided by their referring physicians, such as: I) nephropathy (the pathological condition characterized by the progressive decline in the renal function); II) diabetic retinopathy (a complication of diabetes that has an impact on ocular health); in the present study, individuals with diabetic retinopathy were chosen on the basis of their medical records provided by physicians; III) diabetic neuropathy (a medical condition characterized by nerve damage resulting from diabetes); the selection of participants with diabetic neuropathy in the current investigation was based on their medical records as provided by medical practitioners; IV) diabetic ketoacidosis (DKA; a fatal diabetic complication that poses a risk to life), the individual's blood glucose concentration has exceeded 250 mg/dL. The individual exhibits acidosis, indicated by a blood pH level <7.3, and the presence of ketones in their urine or blood. The present study involved the selection of patients with DKA based on physician reports; V) hypoglycemia (a common issue among individuals with T1DM), which is often caused by the interaction between therapeutic hyperinsulinemia and compromised defenses leading to hypoglycemia-associated autonomic failure. This condition is characterized by glucose levels that fall ≤70 mg/dL (3.9 mmol/L) in individuals with T1DM.

Statistical analysis. The pertinent information was exported to Excel and then entered into GraphPad Prism 7 (GraphPad Software, CA, USA). The data were

assessed for outliers before statistical analysis was carried out. Using descriptive statistics, data were analyzed (for all continuous variables, means and standard deviations [SD] are provided; for scale or nominal data, frequencies and percentages are provided). A 2-way analysis of variance (ANOVA) was used to analyze the variations in laboratory results between study groupings, and the *p*-value of ≤0.05 or 0.001 thresholds of probability was used to determine whether statistical analyses were significant. All statistics were examined between TIDM (control group) and T1DM with autoimmune diseases (uncontrol group). The study utilized the method of multiple logistic regression to assess the association between particular biomarkers, which were considered independent predictor variables, and the heightened occurrence of T1DM and other autoimmune diseases or complications (nephropathy, CVD, and hypoglycemia), which were regarded as outcomes. The model was adjusted for age and gender. The analysis involved calculating the odds ratio (OR) for the 95% confidence intervals (CI). At the level of statistical significance of $p \leq 0.05$.

Table 1 - Descriptive data for type 1 diabetes mellitus patients.

Parameters	Total (n=2258)
Age (years)	
Children (≤12 years)	500 (22.2), 12±2.2
Adolescents (13-17 years)	540 (23.9), 17±1.3
Adults (≥18 years)	1218 (53.9), 29.5±10.5
Duration of T1DM related to age	
Children (≤12 years)	6 (1.5)
Adolescents (13-17 years)	10 (3.7)
Adults (≥18 years)	11 (3.6)
Gender	
Male	909 (40.3)
Female	1349 (59.7)
FBG (3.89-5.50 mmol/L)	15.5±7.7
HbA1c (4.3-6%)	9.9±4.6
LDL-C (2.59-4.11 mmol/L)	5.2±1.4
HDL-C (1.04-1.55 mmol/L)	0.77±0.45
Total cholesterol (5.2-6.2 mmol/L)	6.9±2.8
TG (1.7-2.2 mmol/L)	4.9±1.9
TG/HDL-C (<5)	6.3±0.91
ALP (40-129 U/L)	305.8±33.8
Albumin (3.5-5.0 g/dL)	3.3±1.1
Creatinine (0.3-1.4 mg/dL)	1.6±0.83
BMI (18.5-25.0 kg/m^2)	22.8±8.2

Values are presented as numbers and percentages (%) for age groups and gender, and the mean ± standard deviation (SD) for continuous variables. T1DM: type 1 diabetes mellitus, FBG: fasting blood glucose, HbA1c: hemoglobin A1c, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides, ALP: alkaline phosphates, BMI: body mass index

Results. The study involved the enrollment of 2258 patients with T1DM, comprising individuals across various age groups, including adults, adolescents, and children. Table 1 presents an overview of the fundamental characteristics. However, it is noteworthy that the percentage of individuals who have been diagnosed with T1DM but lack positive autoantibodies was 23.6%, whereas the percentage of individuals with positive autoantibodies was 76.4%. There were 909 (40.3%) men and 1349 (59.7%) women among the participants. The ages of the participants varied batween 12-56 years, with those over 18 years being the most prevalent age group. There were 500 (22.2%) children under the age of 12, 540 (23.9%) adolescents between the ages of 13-17, and 1218 adults over the age of 18 (53.9%) of the population. High levels of FBG, HbA1c, total cholesterol, and triglycerides were present in the majority of participants. Additionally, the patients' ALP and creatinine levels have risen while their albumin levels have decreased, per reference ranges (Table 1). The reference ranges mentioned in Table 1 above or below were regarded as abnormal.

The overall prevalence of T1DM with autoimmune diseases was 67.4% of the study population. The present study carried out an in-depth cross-sectional evaluation of patients' medical records referred by physicians to determine the percentages of antibodies detected in individuals diagnosed with AITD, CD, AI, and APS. The results revealed that 36.9% of patients with AITD exhibited detectable levels of antibodies, while 24.2% of patients with CD, 36.3% of patients with AI, and 37.5% of patients with APS-II exhibited detectable levels of antibodies (the data has not been presented or displayed).

However, different age and gender groups with T1DM have autoimmune diseases at varying prevalence. Table 2 displays the prevalence of the various autoimmune diseases in T1DM patients in relation to gender and age categories. There were differences in prevalence between the genders and different age groups. For example, 25.7% of female patients identified with autoimmune thyroiditis were adults as opposed to 17.3% and 14.7% of female patients diagnosed at younger ages. A diagnosis of autoimmune thyroiditis was carried out in 28.5% of male patients when they were children, 15.9% when they were teenagers, but only 10.8% when they were adults. When compared to adults of both genders, CD had a higher prevalence in children and teenagers. In contrast, both genders' prevalence of AI was higher in the adult age group (23.6% of females and 19.3% of males) than in the children and adolescent age groups.

Patients with APS-II had almost similar outcomes, but adult men were more likely than females to have the disease (28.5% versus 19.7%; Table 2).

The incidence distribution of complications in patients with T1DM was investigated, we determine the existence of complications based on patient records that have been identified by a physician, and we simply determine the frequency. Participants with T1DM and other autoimmune illnesses had higher rates of nephropathy, CVD, and hypoglycemia than those with other complications (Table 3). For instance, as a result, 12.5% of T1DM, 11.2% of autoimmune thyroiditis, 15.6% of AI, and 18% of APS patients have kidney injury. Additionally, as a result, 14.9% of T1DM alone or with 14.5% of autoimmune thyroiditis, 18.7% of AI, and 19.2% of APS-II patients have CVD. Hypoglycemia affects 16.7% of T1DM patients with 13.3% of autoimmune thyroiditis, 23.6% of AI, and 20.2% of APS. However, the frequency of additional complications varied among various autoimmune illnesses (Table 3).

To examine the differences in laboratory findings among the study groups, a 2-way analysis of variance ANOVA was utilized, as outlined in Table 4. The purpose of this analysis was to detect changes in biomarker levels that have a significant influence on the complications of autoimmune diseases across various types. The study found statistically significant differences ($p \leq 0.05$) in various blood biomarkers, such as FBG, HbA1c, total cholesterol, triglycerides, ALP, albumin, and creatinine levels, between individuals with T1DM and those with other autoimmune diseases. These findings are presented in Table 4. Nonetheless, the groups did not exhibit any noteworthy difference in terms of BMI value, low-density lipoprotein-cholesterol, or high-density lipoprotein-cholesterol levels.

Additional analysis was carried out to establish the association between particular biomarkers and the increased prevalence of T1DM and other autoimmune disorders and complications, such as nephropathy, CVD, and hypoglycemia. To achieve this, we employed multiple logistic regression analysis. The objective is to assess the correlation between independent predictor variables (namely, FBG, HbA1c, lipid, antibodies, and C-peptide) and the heightened incidence of T1DM and other autoimmune diseases as outcomes. The model was adjusted for age and gender. The findings of the study indicated a significant positive correlation

Table 2 - Frequency distribution of autoimmune diseases among different gender and age groups with type 1 diabetes mellitus.

Types of autoimmune diseases	Total (N=2258)		Children (≤12 years)		Adolescents (13-17years)		Adults (≥18 years)	
	Female	Male	Female	Male	Female	Male	Female	Male
Only T1DM	450 (33.4)	287 (31.6)	133 (44.3)	58 (29.0)	148 (44.4)	70 (33.8)	169 (23.6)	159 (31.7)
Autoimmune thyroiditis	285 (21.1)	144 (15.8)	52 (17.3)	57 (28.5)	49 (14.7)	33 (15.9)	184 (25.7)	54 (10.8)
Celiac disease	150 (11.1)	119 (13.1)	60 (20.0)	39 (19.5)	37 (11.1)	31 (15.0)	53 (7.4)	49 (9.8)
Adrenal insufficiency	250 (18.5)	162 (17.8)	32 (10.7)	33 (16.5)	49 (14.7)	32 (15.5)	169 (23.6)	97 (19.3)
APS-II	214 (15.9)	197 (21.7)	23 (7.7)	13 (6.5)	50 (15.0)	41 (19.8)	141 (19.7)	143 (28.5)
Total	1349 (59.7)	909 (40.3)	300 (60.0)	200 (40.0)	333 (61.6)	207 (38.4)	716 (58.8)	502 (41.2)

Values are presented as numbers and percentages (%). T1DM: type 1 diabetes mellitus, APS-II: autoimmune polyglandular syndrome II

Table 3 - The frequency distribution of T1DM complications in patients with autoimmune diseases and without.

Types of complications	Only T1DM	Autoimmune thyroiditis	Celiac disease	Adrenal insufficiency	APS-II
Kidney damage (nephropathy)*	92 (12.5)	48 (11.2)	34 (12.6)	64 (15.6)	74 (18.0)
Eye damage (retinopathy)*	114 (15.5)	10 (2.3)	5 (1.9)	41 (10.0)	42 (10.2)
Nerve damage (neuropathy)*	149 (20.2)	33 (7.7)	6 (2.2)	57 (13.9)	55 (13.4)
Ketoacidosis without coma*	103 (14.0)	15 (3.5)	8 (3.0)	56 (13.6)	56 (13.6)
Cardiovascular disease	110 (14.9)	62 (14.5)	22 (8.2)	77 (18.7)	79 (19.2)
Hypoglycemia*	123 (16.7)	57 (13.3)	29 (10.8)	97 (23.6)	83 (20.2)
Without complications	46 (6.2)	204 (47.5)	165 (61.3)	19 (4.6)	22 (5.4)
Total	737 (32.6)	429 (19.0)	269 (11.9)	411 (18.2)	411 (18.2)

Values are presented as numbers and percentages (%). *The current investigation reviewed the diverse complications encountered by individuals diagnosed with T1DM, utilizing their medical records and reports supplied by their referring physicians. T1DM: type 1 diabetes mellitus, APS-II: autoimmune polyglandular syndrome II

Table 4 - Type 1 diabetes mellitus patients with autoimmune disorders and those without were subjected to laboratory tests.

Parameters	Only T1DM	Autoimmune thyroiditis	CD	AI	APS-II	*P*-values
FBG (3.89-5.50 mmol/L)	16.5±7.4	19.5±8.4	14.3±5.7	13.2±4.7	18.8±6.3	0.03*
HbA1c (4.3-6.0%)	10.2±3.6	12.9±5.6	8.9±3.6	8.7±4.6	13.8±5.6	0.03*
LDL-C (2.59-4.11 mmol/L)	5.5±1.2	6.2±1.4	5.6±1.3	5.2±1.4	5.8±1.5	0.06
HDL-C (1.04-1.55 mmol/L)	0.87±0.55	0.78±0.75	0.88±0.55	0.79±0.44	0.79±0.53	>0.05
Total cholesterol (5.2-6.2 mmol/L)	6.7±2.6	7.3±2.6	6.8±2.5	6.9±2.8	6.5±2.82	0.04*
TG (1.7-2.2 mmol/L)	5.1±1.7	5.9±1.9	5.2±1.6	5.5±1.7	5.8±1.6	0.05*
TG/HDL-C (<5)	5.8±1.1	7.5±1.3	5.9±1.2	6.9±1.31	7.3±1.31	0.04*
ALP (40-129 U/L)	310.8±38.2	200±44.8	125.9±38.3	180.8±21.2	245±43.5	0.02*
Albumin (3.5-5.0 g/dL)	3.1±0.87	2.8±0.88	4.1±0.97	4.3±0.94	2.9±1.1	0.02*
Creatinine (0.3-1.4 mg/dL)	1.6±0.83	1.8±0.88	1.5±0.78	1.9±0.87	1.8±0.93	0.05*
BMI (18.5-25.0 kg/m^2)	23.9±5.2	22.3±7.2	23.9±5.2	21.9±6.6	22.6±8.2	0.08

Values are presented as means ± standard deviation (SD). P-values were obtained from 2-way ANOVA. *A *p*-value of ≤0.05. T1DM: type 1 diabetes mellitus, CD: celiac disease, AI: adrenal insufficiency, APS-II: autoimmune polyglandular syndrome II, FBG: fasting blood glucose, HbA1c: haemoglobin A1c, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides, ALP: alkaline phosphatase, BMI: body mass index

between FBG (OR=6.32), HbA1c (OR=6.33), GADA (OR=7.81), ICA (OR=6.66), and IgA (OR=6.71) with the incidence of T1DM at a significance level of $p<0.05$. Conversely, C-peptide exhibited a negative correlation with the incidence of T1DM, with an OR of -6.56. Moreover, the biomarkers FBG, TSH, T4, TOP, and IgA exhibited a positive correlation with the increased occurrence of autoimmune thyroiditis. Conversely, the cholesterol level demonstrated a negative association with the incidence of autoimmune thyroiditis. Table 5 summarizes the biomarkers that exhibited a significant correlation with CD, AI, or APS. Table 5 elucidated the correlations between predictors and the likelihood of experiencing complications such as nephropathy, CVD, and hypoglycemia.

Discussion. A total of 2258 individuals with TIDM, including adults, adolescents, and children, participated in the current study (1349 [59.7%] women and 909 [40.3%] men). The ages of the participants ranged from 12-56, with most of the group being over 18 years old. In 67.4% of this study's participants, T1DM was associated with autoimmune diseases. However, frequency varied by age and gender. Multiple immunologic abnormalities may account for the relatively high incidence of autoimmune disease in T1DM patients. Most organ-specific autoimmune diseases are characterized by atrophy of the organ's lymphocytes and macrophages, which impairs their ability to function. This developing autoimmunity is characteristic of organ-specific autoimmune disorders.[19] According to Aljabri et al[20] the increased frequency of autoimmune disease development in T1DM patients may be due to several immunologic abnormalities. More than 30% of persons with T1DM have additional antibodies that target other organs, such as the thyroid glands, adrenal glands, and small intestine. This can cause hypothyroidism, AI, and CD.

In prior research carried out in Saudi Arabia, 15.8% of infants and adolescents with T1DM were found to have thyroid dysfunction.[21] Approximately 25.7% of female patients with autoimmune thyroiditis were adults, versus 17.3% and 14.4% of female patients diagnosed at younger ages. In 28.5% of cases, male patients were diagnosed with autoimmune thyroiditis as minors, 15.9% as adolescents, and just 10.8% as adults. Hypothyroidism, in particular autoimmune thyroiditis, has been previously linked to more frequent hypoglycemic attacks in diabetic infants.[21,22] In this study, 25.7% of female patients with autoimmune thyroiditis were adults, whereas the prevalence of autoimmune thyroiditis in adult males was minimal (only 10%). Previous research indicates that the prevalence of autoimmune thyroiditis is higher in women and rises with age.[23]

Also, CD was more common in children and teenagers than in adults of both genders. The prevalence of CD among children and adolescents with T1DM in Saudi Arabia has consistently increased and is now estimated to be between 1-16%; this prevalence is among the highest in the world.[24,25] In this study, 11.1% of female patients and 13.3% of male patients were diagnosed with CD. Nevertheless, the prevalence of CD was lower among both adult male and female populations. Consistent with our findings, adolescents have a higher incidence of CD than the general

Table 5 - A multivariate logistic regression model was employed to investigate the potential associations between biomarkers and the incidence of either type 1 diabetes mellitus or other autoimmune diseases.

Parameters	Only T1DM	Autoimmune thyroiditis	CD	AI	PGAS	Nephropathy	CVD	Hypoglycemia
FBG	6.32 (2.22-7.17)	5.32 (1.27-6.17)	5.32 (2.77-6.19)	5.44 (1.47-7.19)	1.24 (0.27-2.17)	6.55 (1.33-7.57)	4.33 (1.77-5.87)	-5.51 (1.37-6.97)
HbA1c	6.33 (2.31-7.27)	1.22 (1.31-2.28)	1.22 (1.21-2.33)	1.21 (1.01-2.08)	2.22 (1.01-2.58)	2.32 (1.21-2.77)	4.44 (1.61-5.28)	-5.44 (1.91-7.28)
Cholesterol	1.11 (1.02-1.44)	-4.44 (1.52-5.44)	1.32 (0.52-2.44)	5.43 (2.54-6.44)	1.11 (0.72-1.44)	3.22 (1.32-4.44)	5.55 (1.62-7.84)	1.12 (0.82-2.04)
Triglycerides	1.32 (0.82-2.07)	2.21 (0.92-3.01)	1.23 (0.98-2.11)	2.11 (1.12-3.11)	2.23 (1.22-3.41)	3.21 (1.82-4.01)	5.66 (1.92-6.90)	1.34 (0.91-2.01)
Albumin	3.21 (1.12-3.87)	1.11 (0.62-1.87)	1.11 (0.82-1.97)	1.11 (0.72-1.97)	0.54 (0.22-1.47)	-5.55 (2.62-6.87)	1.11 (0.72-1.67)	1.14 (0.72-1.47)
Creatinine	3.64 (1.32-4.02)	0.76 (0.52-1.82)	1.21 (0.62-1.94)	2.15 (1.52-2.82)	0.076 (0.42-1.72)	7.65 (2.52-9.92)	1.34 (0.52-1.92)	0.44 (0.32-1.12)
GADA	7.81 (2.52-8.47)	0.78 (0.52-1.47)	0.55 (0.42-1.47)	2.22 (1.42-2.47)	5.44 (1.52-7.27)	3.32 (1.52-4.41)	2.21 (1.52-2.47)	0.54 (0.22-1.17)
ICA	6.66 (1.32-7.87)	0.55 (0.32-1.87)	0.43 (0.32-1.37)	0.86 (0.42-1.77)	3.33 (1.32-3.97)	3.44 (1.32-3.87)	2.45 (1.32-2.87)	0.43 (0.12-1.05)
C-peptide	-6.56 (1.42-8.13)	1.43 (1.12-2.13)	0.87 (0.72-1.73)	2.13 (1.32-2.88)	2.15 (1.15-2.88)	2.18 (1.11-3.13)	1.54 (1.18-2.43)	4.35 (1.52-5.13)
TSH	3.33 (1.22-3.47)	6.54 (1.52-7.87)	0.76 (0.42-1.37)	2.01 (0.52-2.87)	2.9 (1.22-3.15)	0.95 (0.99-1.98)	4.54 (1.66-5.97)	1.61 (1.12-1.97)
T4	3.22 (1.21-3.34)	6.54 (2.21-7.54)	0.56 (0.41-1.54)	3.22 (1.21-3.14)	1.16 (0.71-1.84)	3.33 (1.21-3.54)	5.43 (1.23-8.54)	0.59 (0.21-1.54)
TPO	2.31 (1.02-2.66)	8.55 (1.82-9.66)	1.21 (0.82-1.66)	0.44 (0.22-1.16)	5.34 (1.85-7.66)	3.21 (0.82-3.66)	1.45 (1.02-1.66)	0.73 (0.52-1.66)
anti-tTG	2.33 (1.25-2.87)	1.5 (0.85-2.07)	6.51 (1.95-7.87)	0.32 (0.15-1.17)	3.32 (1.85-4.07)	3.44 (0.85-2.07)	1.32 (0.75-2.77)	1.32 (0.83-2.17)
IgA	6.71 (3.22-8.18)	6.43 (2.27-7.98)	8.65 (2.77-9.99)	5.31 (2.427-6.97)	7.55 (2.27-9.98)	5.43 (2.17-8.08)	1.86 (1.27-2.98)	1.38 (1.11-2.08)
ACTH	2.13 (1.52-3.11)	2.12 (1.62-2.77)	1.22 (0.62-2.27)	-5.55 (1.72-6.877)	2.34 (1.42-3.17)	1.32 (1.42-2.97)	0.44 (0.62-1.77)	0.41 (0.62-1.77)
Cortisol	2.33 (1.12-3.14)	2.11 (1.16-3.24)	1.34 (0.86-1.77)	-6.66 (2.16-7.84)	2.54 (1.10-3.04)	1.44 (1.17-2.32)	4.55 (1.76-5.24)	0.53 (0.46-1.24)
Adrenal 21-OH Ab	2.34 (0.92-2.87)	2.11 (1.52-2.97)	1.22 (1.12-2.27)	7.66 (2.52-8.79)	5.45 (2.58-6.90)	2.25 (1.32-3.09)	0.65 (0.52-1.37)	0.37 (0.53-1.37)

Values are presented as odd ratios (OR) for the 95% confidence intervals (CI). The model was adjusted for age and gender. * $P \leq 0.05$ or 0.001. CD: celiac disease, AI: adrenal insufficiency, PGAS: polyglandular autoimmune syndromes, FBG: fasting blood glucose, HbA1c: hemoglobin A1c, GADA: glutamic acid decarboxylase autoantibody, ICA: Islet cell antibodies, TSH: thyroid-stimulating hormone, T4: thyroxine, TPO: anti-thyroperoxidase, anti-tTG: transglutaminase antibody, IgA: immunoglobulin A, ACTH: adrenocorticotropic hormone, CVD: cardiovascular disease

population. Estimates indicate that adolescents with diabetes have a 20-fold higher prevalence of CD than the general population.[26] These findings validate the investigation carried out by Triolo et al.[27] Their research revealed that 24.6% of diabetic adolescents had CD. In contrast, prior research found no obvious variations in the prevalence of CD among T1DM patients based on age, gender, HbA1c level, hypoglycemia, or the presence of other autoantibodies.[28] However, according to our findings, the prevalence of CD among patients decreased with age.

In the present cohort population, adults were more likely to have AI than children and adolescents (23.6% of females and 19% of males). According to previous reports, the prevalence of T1DM in patients is substantial (0.8-1.2%).[27] The decision to screen for autoimmune AI in T1DM is still up for debate.[28-30] Babiker et al[31] and Mark et al[32] believe that adolescents with T1DM should only have their adrenal antibodies evaluated when a clinical suspicion of AI exists. This may have contributed to the higher prevalence of AI among our adult participants compared to those of a younger age. Adrenal insufficiency is caused by a deficiency in all adrenocortical hormones (aldosterone, cortisol, and androgens) and is frequently associated with other autoimmune disorders. Hypoglycemia can be the initial sign of AI in children and adults, and it can exacerbate glycemic control and necessitate a reduction in the total daily insulin dose in T1DM patients. Therefore, any patient presenting with unexplained hypoglycemia or decreased insulin requirements should be suspected of developing T1DM-related AI.

Autoimmunity against multiple endocrine organs is what makes up APS, which are also called polyglandular autoimmune syndromes (PGAS) because they can affect more than one gland.[33,34] The findings of patients with PGAS were nearly identical across study groups, but adult males were more likely to have the diseases than adult females (28.5% versus 19%). Previously, T1DM with autoimmunity-related polyglandular syndrome was associated with a variety of ethnic groups, including Finns, Sardinians, and Iranians.[33] In most cases, candidiasis is the first clinical symptom to manifest before the age of 5, followed by chronic hypoparathyroidism before the age of 10, and Addison's disease later, usually before the age of 15.[35,36]

Hypoglycemia, nephropathy, and CVD were more prevalent among participants with T1DM and other autoimmune diseases than among those with other complications. Consistent with the findings of

Dailey et al[37] the incidence of hypoglycemia in diabetes was 16.7%, and it was found to be higher in individuals with diabetes combined with autoimmune thyroiditis, AI, and PGAS. In addition, nephropathy was observed in 24 (15.5%) and retinopathy was observed in 86 (55.5%) cases, during a 20-year follow-up period after the onset of T1DM (155 participants completed the entire duration of the follow-up).[38] However, the incidence of nephropathy in T1DM patients with autoimmune thyroiditis was 11.2%, 15.6% with AI, and 18% with PGAS, according to the current study. While the prevalence of retinopathy was lower than that of other complications, this discrepancy was due to the retrospective nature of the study as well as the unknown status and duration of treatment.

Additionally, even in young individuals with T1DM, the incidence of CVD ranges between 1-2% per year; this is true regardless of age. According to glycemic control, T1DM patients have a cardiovascular mortality risk that is up to 10 times that of the general population at age 40 and up to 8 times that of the general population at various ages. More than 70% of males and 50% of females with T1DM have coronary artery calcification by age 45.[41] Consistent with our findings, patients with T1DM had a high prevalence of CVD (14.9%), despite the fact that the incidence increased in patients who also had other autoimmune diseases. Even though the link between diabetes and CVD is well established, the underlying mechanisms remain poorly understood. Earlier research on cardiovascular mortality in T1DM indicated that the risk does not increase significantly until nephropathy develops, which is also when the lipid profile and blood pressure begin to deteriorate noticeably.[42] Blood biomarker levels, including FBG, HA1c, total cholesterol, triglycerides, ALP, albumin, and creatinine, were statistically significantly different between T1DM and other autoimmune disease participants (p<0.05). The majority of subjects had elevated levels of triglycerides, total cholesterol, FBG, and HA1c. In addition, the patients' ALP and creatinine levels have increased in accordance with the reference range, whereas their albumin levels have decreased. All of these potential biomarker modifications can be regarded as CVD predictors. The Pittsburgh epidemiology of diabetes complications study discovered that baseline glycated HbA1c levels, duration of diabetes, lower insulin doses, impaired renal function, increased albumin excretion, higher diastolic blood pressure, and a lipid profile were all indicators of CVD.[43] Based on the entirety of accessible data, it is evident that the combination of T1DM and autoimmune disorders is correlated with a mortality rate that is approximately 3 times higher than that of the overall populace. The correlation between T1DM and other autoimmune diseases has been firmly established in the literature. However, the mechanisms that underlie this relationship are not yet fully comprehended, and there is a tendency to neglect the imperative for improved therapeutic interventions. It is imperative for clinicians to acknowledge that individuals diagnosed with T1DM, regardless of age, exhibit an increased susceptibility to CVD and nephropathy. As a result, there exists a potential avenue for mitigating this lingering risk by enhancing the identification of individuals who are susceptible to adverse outcomes, and innovative interventions could potentially ameliorate the complications associated with T1DM and autoimmune disorders.

Study limitations. Patient information was only gathered from one hospital, so it may not be representative of the whole region. The patients were chosen based on what the doctors saw and what the laboratory tests showed, so it was also not complete. Case-control studies and upcoming prospective studies with a larger sample size from different centers will be needed to learn more regarding autoimmunity in Saudi Arabian children, teenagers, and adults with T1DM. The significance of timely identification of antibodies, biomarkers, and organ-specific dysfunction has been emphasized in recent research. This retrospective and descriptive study aims to encourage healthcare professionals to undertake appropriate measures to prevent the development of full-blown disease and its associated complications.

In conclusion, the prevalence of autoimmune diseases among individuals with T1DM in Saudi Arabia was observed to be substantial, with variations in incidence rates across different age groups and genders. Autoimmune diseases such as CD and autoimmune thyroiditis are commonly observed among young patients diagnosed with T1DM in Al-Madinah Al-Munawwarah. Polyglandular autoimmune syndromes and AI are commonly observed in elderly patients with T1DM. The elevated prevalence of autoimmune disease is associated with various biochemical alterations, notably in parameters such as FBG, HbA1c, total cholesterol, triglycerides, ALP, albumin, and creatinine levels. Cardiovascular disease and nephropathy were identified as the most severe adverse reactions that necessitated prompt treatment and constant monitoring upon initial manifestation of symptoms. It is advisable to carry out routine assessments of individuals with T1DM for autoimmune disorders and associated complications.

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