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Long-term pediatric endocrinological aspects of Coronavirus Disease-19 (COVID-19)

PhD thesis

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACE-2: Angiotensin-converting enzyme 2

ADA: American Diabetes Association

ARDS: Acute respiratory distress syndrome

AIT: Autoimmune thyroiditis

AITD: Autoimmune thyroid disease

Anti-tTG: Anti-tissue transglutaminase

ASIA: Autoimmune/inflammatory syndrome induced by adjuvants

ATG: Antithyroglobulin

ATPO: Anti-thyroid peroxidase

BMI: Body mass index

CD: Celiac disease

CD40: Cluster of differentiation 40

CDC: Centers for Disease Control and Prevention

CGM: Continuous glucose monitoring

COVID-19: Coronavirus disease 2019

CTLA-4: Cytotoxic T-lymphocyte–associated antigen-4

DAISY: Diabetes Autoimmunity Study in the Young

DIPP: Type 1 Diabetes Prediction and Prevention Study

DKA: Diabetic ketoacidosis

DM: Diabetes mellitus

EDCs: Endocrine-disrupting chemicals

EMA: Endomysial antibodies

FCRL3: Fc receptor-like 3

FOXP3: Forkhead box P3

fT3: Free triiodothyronine

fT4: Free thyroxine

GAD-65A: Glutamic acid decarboxylase-65 autoantibodies

GD: Graves' disease

GWAS: Genome-wide association studies

HbA1c: Hemoglobin A1c

HD: Hashimoto's disease

HLA: Human leukocyte antigen

IA-2A: Protein tyrosine phosphatase autoantibodies

IAA: Insulin autoantibodies

ICA: Islet cell antibodies

ICU: Intensive care unit

IFIH1: Interferon induced with helicase C domain 1

IgA: Immunoglobulin A

IgG: Immunoglobulin G

IL2RA: Interleukin-2 receptor alpha chain

INS: Insulin gene

IP4C: International Post-COVID-Condition in Children Collaboration

ISPAD: International Society for Pediatric and Adolescent Diabetes

LC: Long COVID

LCS: Long COVID syndrome

MIS-C: Multisystem inflammatory syndrome in children

NICE: National Institute for Health and Care Excellence

PCC: Post COVID-19 condition

PCR: Polymerase chain reaction

PTPN22: Protein tyrosine phosphatase non-receptor type 22

RAT: Rapid antigen test

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

SAT: Subacute thyroiditis

SWEET: Better control in Pediatric and Adolescent diabete**S**: **W**orking to cr**E**ate C**E**n**T**ers of Reference

T1D: Type 1 diabetes

TA: Thyroid autoimmunity

TEDDY: Environmental Determinants of Diabetes in the Young

TFTs: Thyroid function tests

Tg: Thyroglobulin

TIR: Time in range

TMPRSS2: Transmembrane serin protease 2

TRAb: TSH receptor antibodies

TSH: Thyroid-stimulating hormone

TSHR: Thyroid-stimulating hormone receptor

UK: United Kingdom

ULN: Upper limit of normal

US: United States

WHO: World Health Organization

ZnT8A: Zinc transporter 8 autoantibodies

1. INTRODUCTION

1.1. The Coronavirus Disease-19 pandemic

1.1.1. Epidemiology

In late 2019, a novel coronavirus (Severe acute respiratory syndrome coronavirus 2 /SARS-CoV-2/) emerged, causing a worldwide pandemic that has profoundly changed our lives for years. As of March 23, 2025, a total of 777,684,506 confirmed cases and 7,092,720 deaths have been reported to the World Health Organization (WHO). (1) However, the actual number of infections is likely higher, as these data include only officially registered cases. In Hungary, the total number of reported cases has reached 2,237,977, with 49,124 deaths recorded until March 23, 2025. (1) Initially, children appeared to be less affected by Coronavirus disease-19 (COVID-19). (2) However, increasing evidence has shown that although children are more likely to experience asymptomatic or mild disease than adults, they are not spared from the infection. (3-5) A systematic review from 2023 estimated that by the time of the sixth pandemic wave, approximately 60% of children had been contracted SARS-CoV-2. (6) Pediatric data from Hungary remain limited. Based on statistics from the Hungarian National Public Health Centre, by February 15, 2022 (fifth wave), 236,656 children aged 0-18 years had been registered with confirmed SARS-CoV-2 infection (morbidity rate: 12,974/100,000 children). The highest burden among children was observed during the fourth and fifth waves of the pandemic. (7)

1.1.2. Pathomechanism

The virus enters host cells via its spike glycoprotein, which binds to the angiotensin-converting enzyme 2 (ACE-2) and is activated by transmembrane serin protease 2 (TMPRSS2) to mediate membrane fusion and viral entry. It replicates primarily in the upper respiratory tract, triggering an innate immune response characterized by interferon and cytokine production. (8) If this response is prompt and well-regulated, viral proliferation can be suppressed, limiting disease severity. However, when viral clearance is delayed, dysregulated immune responses may occur, leading to excessive inflammation, immune cell infiltration and widespread tissue damage. (9) This cascade contributes to endothelial activation, microvascular thrombosis, acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. While early damage is often due to

direct viral cytopathy, severe manifestations are largely driven by abnormal host immunity. (10) The broad expression of ACE-2 in multiple tissues (such as the lungs, intestines, pancreas, heart, blood vessels, kidneys and thyroid gland) may contribute to the systemic involvement observed in severe COVID-19 cases. (9, 10)

The acute infection-related symptoms, its diagnosis and outcomes are not discussed here, as they are not directly relevant to the scope of this thesis.

1.1.3. Post-Acute Sequelae

Fortunately, the COVID-19 pandemic seems to subside, but its long-term effects still impact many individuals in various ways which are likely to persist. In pediatrics, the two major late-onset sequelae which should be highlighted are multisystem inflammatory syndrome in children (MIS-C) and long COVID syndrome (LCS).

1.1.3.1. Multisystem inflammatory syndrome in children

Multisystem inflammatory syndrome in children is a rare but serious complication of SARS-CoV-2 infection, characterized by prolonged fever, multi-organ involvement (dermatologic, cardiac, coagulopathic, gastrointestinal and hypotension or shock states) and elevated inflammatory markers. (11) Evidence or strong suspicion of prior COVID-19, along with the exclusion of other potential causes are required for the diagnosis. While most children recover without long-term complications, the condition is associated with a 45% intensive care unit (ICU) admission and a 2% mortality rate. (12) A subset of patients may experience persistent medical problems, such as coronary artery abnormalities. (13)

1.1.3.2. Long COVID syndrome

One of the earliest definitions of LCS or post COVID-19 condition (PCC) was published in December, 2020 by the adult National Institute for Health and Care Excellence (NICE) guideline, which characterized it by new or persistent symptoms lasting more than four weeks following an acute SARS-CoV-2 infection. (14) As this was the only available case definition at the time, we applied it when we established our pediatric long COVID (LC) outpatient clinic at the Bókay Unit of the Pediatric Center in March 2021. The WHO refined this criteria and extended it for children only in 2023, specifying that symptoms should persist for at least three months following the initial infection. (15) However, in 2022, a research (but not clinical) definition for pediatric LCS

has also been developed through Delphi consensus. (16) Nevertheless, the International Post-COVID-Condition in Children Collaboration (IP4C), to which we contributed data, highlighted the substantial heterogeneity in the definition, diagnosis and management of pediatric PCC across countries and institutions. (17)

According to a meta-analysis, its estimated prevalence among children was 16%. (18) In our initial analysis of 89 children with LCS, we observed a girl predominance (63%), with a mean age of 11.4 (± 3.6) years. On average, each child reported 12 symptoms, among which persistent fatigue, loss of interest or pleasure, headache, post-exertional malaise and trouble in concentrating were the most frequent ones. (19) Regarding LCS's pathophysiology, several hypotheses exist including organ damage during acute infection, viral persistence, autoimmune responses and post-viral syndromes of unclear origin (20), but stronger evidence is needed to support the exact mechanisms.

1.1.3.3. Other conditions

Besides MIS-C and LCS, several other conditions have been associated with COVID-19, including autoimmune, cardiovascular and neuropsychiatric disorders. Among these, pediatric autoimmune endocrine diseases are the main focus of my thesis and are discussed in detail in the subsequent sections.

1.2. Type 1 diabetes

1.2.1. Epidemiology

1.2.1.1. International data

Type 1 diabetes (T1D) is one of the most common childhood chronic diseases globally. It is the predominant form of diabetes in the pediatric population, accounting for over 90% of cases. (21) In 2024, the estimated prevalence of T1D in individuals under 20 years of age was 1.81 million. In the same year, 219,000 new diagnoses were reported in children and adolescents. (22) The incidence has been rising in most regions, with an annual average increase of 3-4%. (23, 24) However, in recent years, a deceleration of this trend has also been observed in some high-incidence countries. (23, 25)

A noteworthy geographical variation in the incidence can be observed between countries such as Papua New Guinea and Venezuela (0.1/100,000 children/year) and Finland (52.2/100,000 children/year). (26) According to some studies there is a slight male predominance, while others found no significant differences regarding sex. (27-29) Age at onset varies, with a peak observed in the 10-14-year age group. (28, 29)

Epidemiological patterns observed during the COVID-19 pandemic are a key topic of this thesis and are discussed in detail in a later section.

1.2.1.2. National data

Since 1989, Hungary has participated in the EURODIAB collaboration through the establishment of the Hungarian Childhood Diabetes Epidemiology Network. All pediatric diabetes care centers across the country contribute data annually to the Hungarian Pediatric Diabetes Registry. Over the past decades, the incidence of T1D among children aged 0-14 years in Hungary increased significantly, from 7.7/100,000 children/year in 1989 to 21.9/100,000 children/year in 2018. (30, 31) Based on these trends, Hungary transitioned from a moderate- to a high-incidence country. Over the past few years, however, the annual incidence has remained stable (20.7/100,000 children/year in the most recently available year, 2021, based on data presented at a conference (32)), with a current prevalence of approximately 1 in 600 children.

1.2.2. Etiology, pathophysiology

Type 1 diabetes is a complex disease with multifactorial etiology, most commonly caused by autoimmune destruction of pancreatic β-cells, ultimately leading to absolute insulin deficiency. Its development involves genetic susceptibility, immune dysregulation and environmental exposures. Although numerous genetic and environmental risk factors have been identified, the precise etiology of the disease is still not completely understood. (21, 33, 34)

1.2.2.1. Genetic predisposition

Type 1 diabetes shows familial clustering, proving the role of genetic factors in its etiology. While the prevalence in the general population is approximately 0.4%, it rises to 6-7% among siblings of affected individuals, corresponding to a roughly 15-fold increased risk. (21, 35) Long-term follow-up of monozygotic twins shows a concordance rate of over 60%. (36) The most important region of the human genome associated with T1D is the human leukocyte antigen (HLA) complex, located at the 6p21.3 locus. (37, 38) Alleles within the HLA class II region are responsible for 30-50% of the heritable susceptibility. The strongest associations are observed with HLA-DR and HLA-DQ molecules, which are cell surface receptors involved in antigen presentation to T lymphocytes. (21) In addition to the HLA region, several other genetic loci have been identified relevant in the development of T1D including the insulin gene (INS), cytotoxic

T-lymphocyte–associated antigen-4 (CTLA-4), protein tyrosine phosphatase non-receptor type 22 (PTPN22), interleukin-2 receptor alpha chain (IL2RA) and interferon induced with helicase C domain 1 (IFIH1) as well as multiple further risk loci discovered through genome-wide association studies (GWAS). (21, 34)

1.2.2.2. Environmental factors

Large, prospective cohort studies, including the Environmental Determinants of Diabetes in the Young (TEDDY (39)), Diabetes Autoimmunity Study in the Young (DAISY (40)), and the Type 1 Diabetes Prediction and Prevention Study (DIPP (41)), have investigated various environmental factors that may contribute to the development of T1D. Among these, infectious agents are particularly relevant to the focus of this thesis. Enteroviruses, especially Coxsackie B viruses, are supported by the strongest evidence as environmental triggers contributing to T1D pathogenesis. The presence of enteroviruses has been detected more frequently in multiple tissues of individuals with T1D or those at increased risk. (42-44) Also, several prospective studies have demonstrated a positive association between enterovirus infection and the development of islet autoimmunity and/or T1D. (45-47) Meta-analyses indicate a 5- to 10-fold increased risk in individuals with prior enterovirus exposure. (48-50) Moreover, maternal enteroviral infection during pregnancy has been linked to a higher chance of T1D in the offspring. (51-53) The potential role of SARS-CoV-2 is discussed later in detail. Evidence supporting the involvement of other viral pathogens (such as rotavirus (54), influenza virus (55), herpes simplex virus (56), cytomegalovirus (57), rubella and mumps (58)) is limited. Early-age respiratory infections in general have also been associated with an elevated risk of islet autoimmunity in some studies. (59, 60)

Additional environmental risk factors proposed in the development of T1D include alterations in the intestinal microbiota (reduced microbial diversity), early exposure to cow's milk and the timing of introduction of solid foods or cereals. Other potential contributors include toxins present in food or water, higher birthweight, rapid weight gain and β-cell stress induced by factors such as obesity, puberty, low physical activity, trauma, infections or psychological stress. On the other hand, a few protective factors have also been suggested, including breastfeeding (especially when continued during the introduction of cereals), vitamin D supplementation and the intake of polyunsaturated fatty acids. (39, 61, 62)

1.2.2.3. Stages of type 1 diabetes

Before the onset of clinically overt diabetes, several asymptomatic immunological events occur. The earliest detectable features include the appearance of islet-specific autoantibodies, followed by pancreatic infiltration of autoreactive T cells, ultimately leading to β-cell apoptosis. (63) The main autoantibodies associated with T1D include islet cell (ICA), insulin (IAA), insulinoma-associated antigen-2 (IA-2A), glutamic acid decarboxylase 65 (GAD-65A) and zinc transporter 8 (ZnT8A) antibodies. (63, 64) The progression of T1D is defined by four stages, which are summarized in Table 1. Longitudinal studies have shown that among children with multiple autoantibodies (Stage 1), the cumulative risk of developing clinical T1D is approximately 70% within 10 years, which increases to 85-92% after 15 years and reaches nearly 100% during the person's lifetime. (64-66)

Table 1. Stages of type 1 diabetes and their characteristics

	Stage 1	**Stage 2**	**Stage 3**	**Stage 4**
≥2 islet autoantibodies confirmed	Yes	Yes	Yes	Yes
Dysglycaemia/Abnormal glucose tolerance	No	Yes	Yes	Yes
Hyperglycaemia with/without clinical symptoms	No	No	Yes	Yes
Chronic or complicated type 1 diabetes	No	No	No	Yes

1.2.3. Autoimmune co-morbidities

Children with T1D are at elevated risk for various autoimmune comorbidities, as approximately 25% of them develop at least one additional autoimmune condition. Autoimmune thyroid disease (AITD) and celiac disease (CD) are the most frequent comorbidities, though other autoimmune disorders (such as primary adrenal insufficiency, autoimmune gastritis, connective tissue and dermatological diseases) may also occur, although less commonly. (67, 68)

1.2.3.1. Autoimmune thyroid diseases

The prevalence of AITDs increases with age, reaching approximately 20% in individuals with T1D, the majority of whom have hypothyroidism (Hashimoto's disease /HD/). (68) Anti-thyroid antibodies can be measured in up to 29% of cases. (69-71) Although less common, hyperthyroidism (Graves' disease /GD/) affects approximately 0.5-6% of individuals with T1D, which is still higher than in the general population. (68, 72, 73). The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends screening for thyroid disease shortly after T1D diagnosis, including measurement of thyroid-stimulating hormone (TSH), anti-thyroid peroxidase antibodies (ATPO) and anti-thyroglobulin (ATG) antibodies. In asymptomatic individuals, TSH should be re-evaluated every two years. Annual testing of TSH is advised for those with positive antibodies at diagnosis or with a family history of AITD. In addition, thyroid function should be reassessed sooner if clinically indicated. (68)

1.2.3.2. Celiac disease

The prevalence of CD among children and adolescents with T1D ranges from 1% to 16%, compared to approximately 0.3–1% in the general population. (67, 68, 74) According to the ISPAD protocol, screening for CD is recommended within the first year following diabetes diagnosis and every two to five years thereafter. More frequent testing is advised in case of clinical symptoms or if the patient has a first-degree relative with CD. (68) The American Diabetes Association (ADA) provides more specific guidance, recommending screening at the time of T1D diagnosis, with repeat testing at two and five years, or sooner if symptoms arise. (67, 75) They also note that, while CD may be diagnosed more than a decade after the onset of diabetes, current data are insufficient to determine the optimal screening frequency beyond five years. Current European guidelines recommend using anti-tissue transglutaminase (anti-tTG) immunoglobulin A (IgA) as the initial screening test. A diagnosis of CD can be made without biopsy if anti-tTG IgA levels exceed ten times the upper limit of normal (ULN) and positivity is confirmed by endomysial IgA antibodies (EMA-IgA) in a second sample while the patient is consuming a gluten-containing diet. (76) Total IgA levels should be assessed at the time of CD screening to exclude IgA deficiency and if it is present, immunoglobulin G (IgG)-based serologic testing should be used. It should be noted that a high rate of spontaneous normalization of anti-tTG has been reported in seropositive children without

a confirmed CD diagnosis both in the international literature (77, 78) and among our pediatric patients treated at the Bókay Unit of the Pediatric Center, Semmelweis University. (79)

1.2.4. COVID-19 related data

1.2.4.1. Possible pathomechanisms

Direct effect

Although COVID-19 typically affects the airways and presents with respiratory symptoms, other organs expressing the ACE-2 (targeted by the viral spike protein) can be impacted as well. Experimental studies involving human pancreatic islet cultures and post-mortem samples from those deceased from SARS-CoV-2 infection, have identified the ACE-2 and other viral entry receptors in the endocrine pancreas. (80, 81) Furthermore, SARS-CoV-2 has been shown to infect pancreatic β-cells, with intracellular viral antigens detected. It has also been found that the infection may induce morphological, transcriptional and functional changes, including β-cell death, a reduction in insulin-secretory granules and impaired glucose-stimulated insulin secretion as well. (82-84)

Indirect effect

Systemic SARS-CoV-2 infection can induce immune activation and a cytokine storm, which may disrupt peripheral tolerance or lead to the bystander activation of non-specific lymphocytes, ultimately activating autoreactive B and T cells. Molecular mimicry between viral and self-antigens may also contribute to the autoimmune reaction. Destruction of pancreatic cells and functional impairment may lead to the release of cryptic antigens, promoting immune cell recruitment and local cytokine production. These cytokines, along with the systemic cytokine storm, can impair insulin secretion and induce β-cell apoptosis, while the resulting inflammatory environment contributes to bystander activation and epitope spreading which are well-established mechanisms in the development of islet autoimmunity. (85, 86)

1.2.4.2. Clinical studies

I would like to highlight that prior to the initiation of our study, only a few clinical observations of incidence changes had been published, convincing epidemiological and case-control studies were absent. However, in recent years, the international literature on this topic has been rapidly evolving, which I discuss in this section.

Incidence of type 1 diabetes during the pandemic

Initial publications on the potential association between SARS-CoV-2 infection and T1D reported heterogeneous findings. Several studies observed a rise in new T1D diagnoses in children during the COVID-19 pandemic compared to the pre-pandemic period. (87-89) Tittel et al., however, noted that the increased incidence of T1D in Germany in 2020 was consistent with the previously observed rising trend. (90) In contrast, an Italian study reported a decline in T1D incidence during the early phase of the pandemic. (91) However, over time, larger studies demonstrated that the observed incidence of T1D was even higher than the expected rates based on previous years. (92, 93) These findings were further supported by recent meta-analyses. (94-96)

Change in seasonality

Data from the international SWEET registry (Better control in Pediatric and Adolescent diabete**S**: **W**orking to cr**E**ate C**E**n**T**ers of Reference) also showed an increase in T1D incidence based on data of 92 centers wordwide; however, this rise remained within the expected range based on the 95% confidence interval. Notably, a shift in seasonality was observed: the typical winter peak in new cases was delayed, with incidence peaking instead during the summer and autumn months. (97) I am honored to be involved in this high-impact publication.

Incidence of diabetic ketoacidosis at presentation

Several studies reported a higher proportion of diabetic ketoacidosis (DKA) at the time of T1D diagnosis during the first wave of the COVID-19 pandemic. (98, 99) Subsequent meta-analyses confirmed these findings. (96, 100, 101) It has been hypothesized that the underlying causes are multifactorial, however, reduced access to medical services and hesitancy to seek healthcare due to fear of infection likely played a major role in this phenomenon. (102, 103)

Metabolic status of children with type 1 diabetes

Data from the SWEET registry showed a higher frequency of DKA while hemoglobin A1c (HbA1c) levels remained stable among children with known T1D. (104) Further data on HbA1c levels showed inconsistent results. (105, 106) However, time in range (TIR) and other continuous glucose monitoring (CGM) metrics improved during the pandemic. (107, 108) Accordingly, a recent meta-analysis found no significant difference in HbA1c

levels but described a significant increase in TIR in patients (including both adults and children) when comparing the lockdown period to pre-pandemic years. (109) The beneficial role of telemedicine in continuous patient management was emphasized in several publications. (108, 110, 111)

Autoantibody negative cases

At the beginning of the pandemic, a case study described a young male patient with preceding COVID-19 who was diagnosed with autoantibody-negative insulin-dependent diabetes mellitus, suggesting a non-autoimmune form of diabetes potentially caused by direct β-cell damage. (112) This was followed by a German multicenter analysis covering the data of more than 6,000 children and young adults which found no evidence of a significant increase in the incidence of autoantibody-negative T1D. (113)

Risk of new-onset type 1 diabetes after SARS-CoV-2 infection

Two studies conducted in the United States (US) and Belgium during the first year of the pandemic indicated no significant difference in the prevalence of SARS-CoV-2 antibodies between children with T1D and the general pediatric population. (114, 115) Since then, several large-scale studies (primarily from the US) found an association between SARS-CoV-2 infection and newly diagnosed T1D (116-119), while others did not demonstrate such a connection. (120-122) Meta-analyses including overlapping pediatric cohorts have demonstrated an elevated risk of T1D onset following SARS-CoV-2 infection. (123-125) In 2020, the CoviDIAB Project was launched to document cases of COVID-19-related diabetes. (126) Our department also contributed data to the global registry, but, interestingly, we are not yet aware of any published results.

Effect of vaccination

A few adult case reports described new-onset autoimmune diabetes following different types of COVID-19 vaccines. (127) However, a population-based cohort study found no significant increase in the risk of T1D in adults after vaccination. (128)

1.3. Autoimmune thyroiditis

1.3.1. Subtypes

The two major types of AITD are HD and GD, however, there is a considerable overlap between these two conditions. Their characteristics are presented in Table 2, with data primarily derived from *Brook's Pediatric Endocrinology, 7th Edition*. (129)

Table 2. Characteristics of pediatric Hashimoto's thyroiditis and Graves' disease

TRAb: TSH receptor antibodies, TSH: Thyroid-stimulating hormone, fT3: Free triiodothyronine, fT4: Free thyroxine, ATPO: Anti-thyroid peroxidase, ATG: Antithyroglobulin

	Hashimoto's thyroiditis	**Graves' disease**
Importance	Most common acquired thyroid disease in childhood	Most common cause of hyperthyroidism in children
Sex distribution	Female predominance	Female predominance
Age at onset	Typically adolescence	Typically adolescence
Patophysiology	Lymphocytic infiltration causes cytotoxicity, apoptosis and autoantibody production. Cytokines further contribute to tissue damage, leading to follicular destruction.	TRAb antibodies stimulate the TSH receptor, causing thyroid hyperstimulation and follicular growth. Lymphocytic infiltration and B-cell dysregulation contribute to glandular enlargement.
Clinical feautres	Fatigue, dry skin, cold intolerance, constipation, hair loss/thinning, decelerated growth, weight gain, bradycardia, delayed puberty, irregular menses	Hyperactivity, insomnia, poor concentration, tachycardia, tremor, heat intolerance, sweating, muscle fatigue, poor weight gain/weight loss despite an increased appetite, accelerated growth, thyroid eye disease, delayed puberty, secondary amenorrhoea
Thyroid function at presentation	(Sub)clinical hypothyroidism (raised TSH, low fT4) or *euthyroidism* or *transient hyperthyroidism*	Hyperthyroidism (suppressed TSH, elevated fT3, fT4)
Autoantibodies	ATPO, ATG	TRAb *(ATPO, ATG)*
Ultrasound characteristics (130, 131)	Enlargement, hypoechogenicity, heterogeneous texture, normal/increased/decreased vascularity, pseudonodularity	Diffuse, symmetrical enlargement, hypoechogenicity, heterogeneous texture, increased vascularity
Treatment	Hormone replacement (levothyroxine)	Anti-thyroid drugs (e.g. thiamazole or propylthiouracil), surgery or *radioactive iodine*

1.3.2. Terminology

Thyroid autoimmunity (TA) is a broad term, defined by the presence of at least one positive thyroid autoantibody (ATPO and/or ATG) detected through laboratory testing, without necessarily showing inflammatory changes on thyroid ultrasound. Thyroiditis is identified via ultrasound by observing glandular enlargement, inhomogeneity or increased vascularity (hyperemia). Autoimmune thyroiditis (AIT) is diagnosed when both a positive autoantibody and ultrasound features consistent with thyroiditis are present.

1.3.3. Epidemiology

The incidence of GD in children ranges between 0.1 and 5.0 per 100,000 per year, with several studies reporting increasing trends over time. (132, 133) It most commonly affects girls and typically presents between the ages of 10 and 15 years. (132, 134) In contrast, the epidemiology of HD is more difficult to define due to its often subtle or asymptomatic presentation, but it is estimated to affect approximately 1-2% of the pediatric population. (135) In cohorts of Spanish and Greek children, the prevalence of AIT was reported to be 1.4% and 2.5%, respectively, with higher rates observed among females and during puberty. (136, 137)

1.3.4. Etiology, pathophysiology

Although the exact etiopathogenesis of AITD remains unclear, it is known to involve a complex interaction of genetic susceptibility, epigenetic modifications and environmental factors.

1.3.4.1. Genetics, epigenetics

Studies in monozygotic twins suggest a major role for genetic predisposition in the development of AITD. (138, 139) These conditions are linked to polymorphisms in both thyroid-specific genes (for example thyroglobulin /Tg/ and thyroid-stimulating hormone receptor /TSHR/) and immunoregulatory genes involved in self-tolerance, including forkhead box P3 (FOXP3), interleukin-2 receptor alpha chain (IL2RA), cluster of differentiation 40 (CD40), CTLA-4, PTPN22, Fc receptor-like 3 (FCRL3) and various HLA subtypes. Among these, HLA-DR3 polymorphisms are associated with the highest genetic risk. (129, 140, 141) Additionally, epigenetic modifications, such as altered DNA methylation patterns, which influence gene expression without changing the DNA sequence, may also contribute to AITD pathogenesis. (142)

1.3.4.2. Environmental factors

Several environmental factors have been implicated in the pathogenesis of AITD. (143) Among infectious agents, in addition to SARS-CoV-2 (which will be described later), Epstein-Barr virus (144), Parvovirus B19 (145), Human Herpesvirus 6A (146) and Helicobacter pylori (147) are most strongly linked to the disease. Higher iodine (148, 149) and lower selenium intake (150), altered gut microbiota composition (151), as well as several medications (including interferon-α, amiodarone, lithium and tyrosine kinase inhibitors (143)) have been suggested to influence the development of TA as well. Excessive iodine consumption is thought to enhance the immunogenicity of Tg through increased iodination. (152) Some studies have found associations between vitamin D deficiency or insufficiency and AITD development (153, 154), while others reported no significant link. (155, 156) Psychological stress has also been connected to an elevated risk of AITD in some cohorts, though other studies, such as the prospective Amsterdam AITD Cohort, found no association with de novo ATPO positivity. (157, 158) Emerging evidence also suggests a potential role for endocrine-disrupting chemicals (EDCs) in both the onset and progression of AITD, although research in this area is still evolving. (159)

1.3.5. COVID-19 related data

1.3.5.1. Possible pathomechanisms

Emerging literature indicates that thyroid dysfunction associated with SARS-CoV-2 infection may arise via multiple, potentially overlapping mechanisms. The proposed pathophysiology involves both direct cytopathic effects and indirect immune-mediated pathways. (160-162) Similar to T1D, SARS-CoV-2 has been shown to infect thyroid follicular cells through ACE-2, which is expressed in thyroid tissue, thereby enabling direct cellular damage. (163, 164) In parallel, the virus may contribute to immune dysregulation, leading to the development or exacerbation of AITD. Indirect mechanisms include: molecular mimicry, bystander activation, epitope spreading, disruption of immunoprivileged barriers and polyclonal lymphocyte activation. These processes may result in both acute and chronic thyroid disturbances. (160, 162)

1.3.5.2. Clinical studies

Besides T1D, several other autoimmune diseases (such as AITD, rheumatoid and juvenil idiopathic arthritis, vasculitis, systemic lupus erythematosus, inflammatory bowel diseases, CD) have been linked to SARS-CoV-2 infection. (165, 166) Among these, my

PhD research focused on AITD. I would like to emphasize that prior to the initiation of our study, only a few case reports and small-scale studies had addressed this topic as well. Since then, an increasing number of clinical studies have highlighted a potential bidirectional relationship between COVID-19 and thyroid disorders.

Thyroid diseases in general

On one hand, evidence suggests that having a thyroid disorder as a chronic comorbidity increases the risk of severe COVID-19. (167, 168) On the other hand, thyroid abnormalities (specifically non-thyroidal illness syndrome (169-171), subacute thyroiditis (SAT) (172-174), painless thyroiditis (174-176), AITD (177-179) could occur as a complication both during and after an acute SARS-CoV-2 infection, as several studies have described. It should be mentioned that the overwhelming majority of articles on COVID-19-related thyroid disturbances published to date present data on the adult population.

Autoimmune thyroid diseases – adult studies

The reactivation or worsening of pre-existing AITDs, as well as the emergence of new-onset HD (180-182) and GD (183-185) following COVID-19, have drawn attention to a possible autoimmunity-triggering or -accelerating effect of the virus. A few studies have described thyroid autoantibody positivity both in the acute phase of COVID-19 and during follow-up assessments. (186, 187) Based on the data of 660 subjects, Rossini et al. reported a higher prevalence of ATPO positivity among COVID-19 survivors (15.7%) than in controls (7.7%). (188) In addition, a Spanish study noted an increased incidence of GD during the pandemic. In 2021, the total number of cases (n=66) was twice as high as in 2020 and 2.44 times greater than the average number of cases reported between 2017 and 2019. (189) However, Goyal et al. did not find a significant difference in the proportion of TA development between 100 infected and 122 non-infected women. (190) Additionally, a follow-up study observed only incidental cases of TA in 250 adults surviving COVID-19. (191)

Autoimmune thyroid diseases – pediatric studies

As it is already mentioned, although children are generally less affected by the acute complications of COVID-19, the disease's long-term burden may significantly impact their lives. Still, data on the relationship between SARS-CoV-2 infection and thyroid

disorders among pediatric population is limited. In a study of 390 children with COVID-19, pre-existing diagnosis of hypothyroidism was associated with an increased risk of hospital and ICU admission. (192) No significant change in the presentation of thyroid dysfunction before and during the pandemic was found according to two retrospective analyses of 244 and 233 children's data. (193, 194) One of these studies did not provide data on TA frequency, while the other reported ATPO levels only among hypothyroid patients, not in the general population. In the first publication from our Pediatric Long COVID research group, we documented a notable rate (12%) of TA among 89 children with LCS. (19) Additionally, two studies specifically examined the prevalence of TA in children with newly diagnosed T1D, but reported conflicting results. (195, 196) Besides these, a few pediatric case reports have been published of children diagnosed with AITD following COVID-19. (197-200) As outlined in a narrative review addressing the impact of COVID-19 on thyroid diseases in children, no definitive evidence demonstrates a link between SARS-CoV-2 infection and an increased incidence of TA in the pediatric population. (201) The authors also emphasized the scarcity of data available on the youth. However, a very recent retrospective observational big data study covering a cohort of over 1.5 million children found that both the incidence rate of GD and hypothyroidsm (including HD) increased during the pandemic years. (165) Still, it remains clear that there is a significant need for longitudinal and well-controlled pediatric research on this topic.

Effect of vaccination

Since the introduction of COVID-19 vaccination, numerous case reports and cohort studies have described SAT (202-204) and AITDs (primarily GD (189, 205, 206)) following the administration of various vaccines. It is assumed that either cross-reactivity (between the viral spike protein and thyroid follicular cell antigens) or autoimmune/inflammatory syndrome induced by adjuvants (ASIA) might be responsible for this phenomenon. (207, 208) However, recent population-based studies have found no increased risk of thyroid dysfunction, SAT, GD or other forms of thyroiditis in vaccinated adult populations. (209-211) Moreover, another adult large-scale study suggests that COVID-19 vaccination may have a protective effect on the incidence of GD. (212) Yet, there is also a lack of data regarding thyroid disorders following COVID-19 vaccination in the pediatric population.

2. OBJECTIVES

2.1. Study I (Anti-SARS-CoV-2 seropositivity among children with newly diagnosed type 1 diabetes mellitus: a case-control study)

1. The primary aim of our study was to assess the prevalence of a positive history of COVID-19 in newly diagnosed T1D patients hospitalized during the third wave of the pandemic and to compare these results with a control group of non-vaccinated, otherwise healthy children with known T1D.
2. We also aimed to evaluate the rates of autoimmune comorbidities and diabetes-specific autoantibodies in these children.

2.2. Study II (Thyroid disturbances after COVID-19 and the effect of vaccination in children: a prospective tri-center registry analysis)

1. The primary purpose of this study was to evaluate the prevalence of anti-thyroid antibody positivity, abnormal thyroid function tests (TFTs) and ultrasound-confirmed thyroiditis in the post-COVID period in children.
2. The secondary aim was to examine the relationship between TA and various factors (e.g., COVID-19 vaccination and LCS status and symptoms).
3. Thirdly, we aimed to assess the persistence of initial anti-thyroid antibody positivity and abnormal thyroid function.

2.3. Study III (Increasing prevalence of thyroid autoimmunity in childhood type 1 diabetes in the pre-COVID but not during the COVID era)

1. Our main objective was to evaluate the annual prevalence of TA in pediatric patients with T1D over a 10-year period, encompassing both pre-pandemic and COVID-19 pandemic years.
2. We also aimed to examine the rate of ultrasound positivity and data on thyroid medication usage among these children.

3. METHODS

3.1. Study I (Anti-SARS-CoV-2 seropositivity among children with newly diagnosed type 1 diabetes mellitus: a case-control study)

3.1.1. Study design and setting

In our case-control study, we examined all children (0-18 years of age) hospitalized between March 1 and June 15, 2021, with new-onset T1D at the Bókay Unit of the Pediatric Center, Semmelweis University, Budapest, Hungary. Anti-SARS-CoV-2 spike antibodies were tested and the positivity rate was compared to a control group. Additionally, newly diagnosed children were routinely screened for autoimmune comorbidities and their results were compared to those diagnosed in the pre-pandemic year.

3.1.2. Patient selection

Study Group: A total of 26 children were admitted with new-onset T1D during our study period. Twenty-one of them agreed to participate in SARS-CoV-2 testing.

Control Group A: Non-vaccinated, otherwise healthy children with known T1D who were admitted for their regular annual checkup to the same Diabetes Department during June and July 2021. Out of them, twenty-two were tested for anti-SARS-CoV-2 on a voluntary basis.

Vaccinated children were excluded from both groups to avoid misinterpretation of serology results.

Control Group B: Patients admitted to our Diabetes Department with newly diagnosed T1D between March 1, 2019 and February 28, 2020 (the last pre-pandemic year). A total of 52 patients were included in this group.

3.1.3. Data collection, measured parameters

Data were collected from the institutional e-MedSolution software. Antibodies against the SARS-CoV-2 spike protein were measured using the Electrochemiluminescence Immunoassay (Elecsys, Roche). Tests were performed at the time of admission or within three months after discharge to confirm or rule out previous COVID-19 infection (screenings were executed between May 11 and July 9, 2021).

All new patients were routinely screened for autoimmune thyroiditis (ATPO and ATG), celiac disease (anti-tTG IgA and IgG), anti-adrenal autoantibodies, as well as four

autoantibodies specific for T1D (GAD-65A, IAA, IA-2A and ZnT8A). We interpreted celiac screening as positive if the titer of anti-tTG IgA was more than three times above the normal range, as the chance of normalization drops remarkably above this level. (78, 213) Ranges of normal values and laboratory methodology can be seen in Table 3.

Table 3. Laboratory assay methodology and normal value ranges (Study I)

CLIA: Chemiluminescence Immunoassay, ECLIA: Electro-chemiluminescence Immunoassay, ELISA: Enzyme-linked Immunosorbent Assay

Laboratory parameter	Assay methodology, manufacturer	Units of measurement	Upper limit
Anti-SARS-CoV-2 spike antibody	ECLIA (Elecsys® Anti-SARS-CoV-2 S assay, Roche), reference number: 09289267190	U/mL	0.8
Anti-thyroid peroxidase (ATPO)	CLIA, Abbott	U/mL	5.6
Antithyroglobulin (ATG)	ECLIA, Roche	UI/mL	115
Anti-transglutaminase IgA (anti-tTG IgA)	ELISA, Inova	U	20
Anti-transglutaminase IgG (anti-tTG IgG)	ELISA, Inova	U	20
Anti-glutamic acid decarboxylase-65 (GAD-65A)	ELISA, Euroimmun	IU/mL	10
Anti-insulin (IAA)	ELISA, Euroimmun	U/mL	12
Anti-protein tyrosine phosphatase (IA-2A)	ELISA, Euroimmun	IU/mL	10
Anti-zinc transporter 8 (ZnT8A)	ELISA, Euroimmun	RU/mL	15

3.1.4. Statistical analysis, ethics

Statistical analysis was conducted using GraphPad Prism software, Version 8.0.1. The level of significance was set a priori at 0.05. We presented normally distributed data as mean (SD), while non-normally distributed data as median (IQR). We used descriptive statistical methods, Kolmogorov-Smirnov normality test, Chi-squared test, Chi-squared test for trend, unpaired t-test and Mann-Whitney test to assess our results. We calculated odds ratios to compare the anti-SARS-CoV-2 positivity rate between newly diagnosed patients and children with previously diagnosed T1D.

Our study has been performed in accordance with the ethical standards set by the Institutional Review Board and the Declaration of Helsinki. Details that might disclose the identity of the subjects were omitted.

3.2. Study II (Thyroid disturbances after COVID-19 and the effect of vaccination in children: a prospective tri-center registry analysis)

3.2.1. Study design and setting

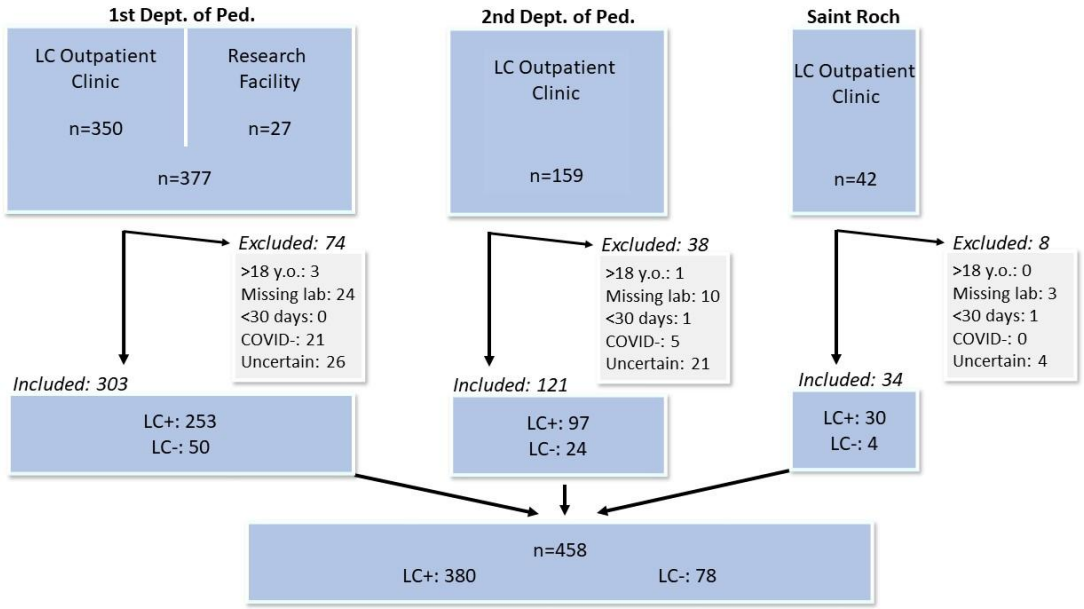
This multicenter, prospective study was carried out at three pediatric Long COVID (LC) outpatient clinics of Semmelweis University, Budapest, Hungary. Children without LCS symptoms were also invited for endocrine screening at the 1st Department of Paediatrics (Bókay Unit of the Pediatric Clinic) for research purposes. The first visits occurred between March 24, 2021 and March 23, 2022. Thyroid laboratory parameters (autoantibodies and functional tests) were measured for all children as a screening regardless of their symptoms. In cases of abnormal results, patients were referred to a pediatric endocrinologist for follow-up. Children not requiring further monitoring according to the specialist were also contacted for re-evaluation. Follow-up visits took place a minimum of two and a maximum of 19 months later, with data included in the current analysis until December 23, 2022.

3.2.2. Patient selection

We included all children (< 18 years of age) with confirmed prior SARS-CoV-2 infection (positive polymerase chain reaction /PCR/, rapid antigen /RAT/ or serology /anti-spike and/or anti-nucleocapsid antibody/ test). Anti-spike antibodies were accepted as proof of infection only in non-vaccinated children. The flowchart of patient inclusion and exclusion criteria can be seen in Figure 1. Enrolled patients were divided into two groups according to their LCS status:

- LC+: children who developed one or more new or worsened symptom(s) after their SARS-CoV-2 infection, which were still present at their first visit (LCS).
- LC-: children with confirmed COVID-19 who were not experiencing any ongoing symptoms related to the previous infection or were symptom-free during their first examination.

Figure 1. Flowchart of patient inclusion and exclusion



Source: own published paper (214)

Dept.: Department, Ped.: Pediatrics, LC: long COVID, LC+: children with long COVID syndrome, LC-: children without long COVID syndrome, >18 y.o.: individuals aged ≥18 years, Missing lab: children who had one or more missing thyroid laboratory results, <30 days: whose examinations were conducted less than 30 days following their COVID-19, COVID-: those who did not have a proven acute infection and whose serology tests were negative, Uncertain: children whose infection status could not be definitively confirmed due to prior vaccination and the absence of anti-nucleocapsid antibody results

3.2.3. Data collection, measured parameters

Standardized data were prospectively collected from all children based on the available WHO guideline. (215) Parents completed a detailed questionnaire, which was verified by a medical doctor, followed by physical examinations and uniform laboratory tests. Clinical data were stored in REDCap (Research Electronic Data Capture) platform hosted at Semmelweis University (216, 217), while laboratory results were retrieved from the institutional e-MedSolution software.

Collected parameters included: visit dates, clinical data (sex, birth date, height, weight, thyroid history), acute SARS-CoV-2 infection details (date, method of proof, severity), COVID-19 vaccination status and date, persisting symptoms, thyroid laboratory values

(ATPO, ATG, TSH and free thyroxine /fT4/ if TSH was altered), ultrasound results, necessity and type of thyroid medication. Body mass index (BMI) Z-scores were calculated from national child growth data (218). COVID-19 severity was assessed using the WHO's classification. (219) Laboratory methods and normal value ranges are shown in Table 4. The test method used for the measurement of ATPO was changed during our study period, therefore we calculated and presented the relative ATPO values as well.

Table 4. Laboratory assay methodology and normal value ranges (Study II)

Source: own published paper (214)

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, CLIA: Chemiluminescence Immunoassay, ECLIA: Electro-chemiluminescence Immunoassay, ELISA: Enzyme-linked Immunosorbent Assay

Laboratory parameter	Assay methodology, manufacturer	Units of measurement	Lower limit	Upper limit
Anti-thyroid peroxidase (ATPO)				
until 11th of January, 2022	CLIA, Abbott	U/mL	-	5.6
from 12th of January, 2022	ECLIA, Roche	U/mL	9	34
Antithyroglobulin (ATG)	ECLIA, Roche	UI/mL	-	115
TSH receptor antibodies (TRAb)	ECLIA, Roche	IU/L	-	1.75
Thyroid-stimulating hormone (TSH)	CLIA, Siemens	mU/L	0.35	4.94
Free thyroxine (fT4)	CLIA, Siemens	pmol/L	9	23.2
Anti-SARS-CoV-2 spike antibody	ECLIA (Elecsys® Anti-SARS-CoV-2 S assay, Roche), reference number: 09289267190	U/mL	-	0.8
Anti-SARS-CoV-2 nucleocapsid antibody	ELISA (GA CoV-2 IgG+, Generic Assay), reference number: 3940	BI (binding index)	-	1.2

To further describe the persistence of the identified non-physiological results, we differentiated between transient (normalization within six months) and long-lasting (parameters remaining abnormal for more than six months) alterations.

3.2.4. Statistical analysis, ethics

Descriptive statistics were reported as means, standard deviations and relative frequencies. Group differences were examined using an independent samples t-test and Fisher's exact test with the phi coefficient was used to measure associations. Since autoantibody levels followed log-normal distributions, standard logarithms were applied for plots and mean effect estimation. The mean effect of time on autoantibody changes was estimated using a generalized least squares method with linear relations and an autoregressive correlation structure. Model fit was assessed with simulation diagnostic plots using the DHARMa package. Statistical calculations were performed using IBM SPSS Statistics (Version 28.0) and R software (v4.2.1 (220)), with the nlme (v3.1.157 (221)), DHARMa (R-DHARMa) and ggplot2 (v3.3.6 (222)) packages.

The study was carried out in accordance with the Declaration of Helsinki and received approval from the Hungarian Medical Research Council (ETT-TUKEB, IV/5943–1/2021/EKU). Informed consent was obtained from the parents of all children included in our research facility.

3.3. Study III (Increasing prevalence of thyroid autoimmunity in childhood type 1 diabetes in the pre-COVID but not during the COVID era)

3.3.1. Study design and setting

This single-center retrospective cohort study was performed at the Bókay Unit of the Pediatric Center, Semmelweis University, Budapest, Hungary. We reviewed the data of all patients with diabetes mellitus (DM) who received insulin treatment and had at least one visit between January 1, 2013 and December 31, 2022, at our Endocrinology and Diabetes Department. The pre-pandemic period was defined as 2013 to 2020 and the pandemic period as 2021 to 2022. In 2020, we expected no or minimal pandemic impact on our results, as a national study indicated only very few pediatric COVID-19 cases during the first wave. (223)

3.3.2. Patient selection

Medical records were obtained using the BNO classification system, which is the Hungarian adaptation of the ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision) developed by the WHO. (224)

Inclusion criteria: Children and young adults (aged 0-21 years) treated for T1D at our center between 2013 and 2022 who had at least one simultaneous ATPO and ATG measurement during the study period. Data on TA were collected from both newly diagnosed patients and those in follow-up care.

Exclusion criteria: Patients over 21 years of age, those with diabetes types other than T1D and those who never underwent TA screening.

3.3.3. Data collection, measured parameters

Clinical data and laboratory parameters were retrieved from Semmelweis University's e-MedSolution software. Data were verified and completed by four doctors and two medical students according to our research protocol. We collected data on sex, date of birth, T1D diagnosis, visit dates, thyroid autoantibody (ATPO, ATG) and TFTs (TSH and fT4) levels of all patients. For antibody-positive children, thyroid ultrasound findings were also obtained. Laboratory analyses were conducted at the Immunology Laboratory of Semmelweis University. Assay methodology and normal ranges can be found in Table 5. If a child had multiple tests in a calendar year, we used the most recent data. Clinically relevant TSH levels were defined as above 6 mU/L or below 0.1 mU/L and/or results that were abnormal at least twice in a patient.

Assessment of autoantibody results

Thyroid autoantibody screening frequencies were based on ISPAD's guidelines (last revised in 2022 (68)), with primarily bi-annual assessment for children without thyroid comorbidities and yearly evaluation for those with previously diagnosed TA. Due to varying screening frequencies for these two groups, the prevalence data would be inaccurately high without adjustment. Therefore, in years when no laboratory tests were performed, we utilized the following protocol:

If antibody titers were negative in both the previous and subsequent years, we considered the intermediate year negative as well. We applied the same approach for positive cases. If the results differed, the intermediate year was treated as missing data.

Table 5. Laboratory assay methodology and normal value ranges (Study III)

Source: own published paper (225)

CLIA: Chemiluminescence Immunoassay, ECLIA: Electro-chemiluminescence Immunoassay, ELISA: Enzyme-linked Immunosorbent Assay

Laboratory parameter	Test used during the study period	Assay methodology, manufacturer	Units of measurement	Lower limit	Upper limit
Anti-thyroid peroxidase (ATPO)					
	January 1, 2013 -	ELISA, Aesku	UI/mL	-	40
	March 25, 2014 -	ECLIA, Roche	U/mL	-	63
	January 21, 2017 -	CLIA, Abbott	U/mL	-	5.6
	January 12, 2022 -	ECLIA, Roche	U/mL	9	34
Antithyroglobulin (ATG)					
	January 1, 2013 -	ELISA, Aesku	UI/mL	-	120
	March 25, 2014 -	ECLIA, Roche	UI/mL	-	115
Thyroid-stimulating hormone (TSH)					
		CLIA, Siemens	mU/L	0.35	4.94
Free thyroxine (fT4)					
		CLIA, Siemens	pmol/L	9	23.2

3.3.4. Statistical analysis, ethics

MedCalc Statistical Software version 22.023 (MedCalc Software bv, Ostend, Belgium; 2020) was used to calculate and compare prevalence data and perform descriptive statistics. Chi-squared comparisons were conducted using StataCorp (Stata Statistical Software: Release 18.5). Visualization was created with Microsoft Excel (Microsoft Corporation, 2016).

The study followed the Declaration of Helsinki, ethical approval was not required due to its retrospective nature.

4. RESULTS

4.1. Study I (Anti-SARS-CoV-2 seropositivity among children with newly diagnosed type 1 diabetes mellitus: a case-control study)

4.1.1. Patient characteristics

A total of 26 children were admitted to our clinic between March 1 and June 15, 2021 with new-onset T1D. In comparison, there were 12 admissions during the same period in 2019 and an average of 17 admissions during the identical months of the pre-pandemic five years (2015–2019). The mean age of children in the study group was 8.5 (± 5.0) years (range: 7 months - 17 years), 16 (61.5%) of them were male. A detailed presentation of their individual data can be found in Table 6. The rate of DKA at admission was 13/26 (50%). Twenty-two control subjects (known T1D patients) were included in the study (control group A) with a mean age of 10.4 (± 3.5) years (12 boys, 10 girls). Control group B consisted of 52 children (65.4% boys), whose mean age was 8.3 (± 4.4) years.

4.1.2. Anti-SARS-CoV-2 testing

We performed the anti-SARS-CoV-2 spike antibody test in 21 of 26 newly diagnosed T1D patients. We ruled out children who refused to be tested or had already been vaccinated to avoid misinterpretation of the serology results. Eleven of the 21 tests showed positive results, representing 52.4% [95%CI: 29.1-75.7] of the tested children. Among children with preexisting T1D (control group A, n=22), we found five patients (22.7%, [95%CI: 3.7-41.7]) with serological evidence of previous COVID-19 (Figure 2). Thus, the newly diagnosed patients had a significantly higher rate of anti-SARS-CoV-2 positivity as compared to known T1D patients (p=0.04) with an odds ratio of 3.74 [95% CI: 1.08-13.55].

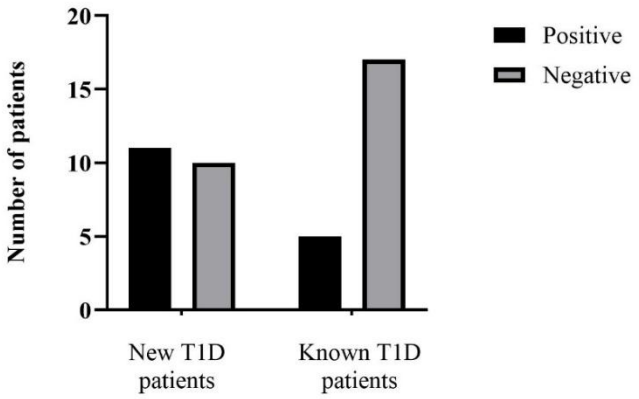
None of the new T1D children with a positive serology had any coronavirus specific symptoms at the time of admission nor they had known anamnesis for COVID-19, as reported by their parents. Additional characteristics of the two groups are presented in Table 7.

Table 6. Characteristics of children with newly diagnosed type 1 diabetes mellitus in 2021

M: male, F: female, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, GAD-65A: glutamic acid decarboxylase-65 autoantibodies, IA-2A: protein tyrosine phosphatase autoantibodies, IAA: insulin autoantibodies, ZnT8A: zinc transporter 8 autoantibodies

	Age (year)	Sex	Month of admission	SARS-CoV-2 antibody	Autoimmune comorbidities			T1D specific autoantibodies			
					Celiac	Thyroid	Adrenal	GAD-65A	IA-2A	IAA	ZnT8A
1.	8.6	M	March	+	-	-	-	+	+	-	+
2.	13.1	F	April	+	+	-	-	+	+	-	-
3.	13.4	M	April	+	-	-	-	+	+	-	+
4.	9.4	F	April	+	+	-	-	+	+	-	+
5.	13.0	F	April	+	-	-	-	-	+	-	-
6.	11.9	M	May	+	-	+	+	+	+	-	+
7.	2.7	F	May	+	+	-	-	-	+	-	+
8.	12.4	F	May	+	-	+	-	+	-	-	-
9.	8.2	F	May	+	-	-	-	+	+	-	-
10.	4.1	F	June	+	+	-	-	+	+	-	+
11.	6.7	F	June	+	-	+	-	+	+	-	+
12.	15.9	M	March	-	-	-	-	+	+	-	+
13.	1.1	M	March	-	-	NA	-	+	+	-	-
14.	12.5	M	April	-	+	+	-	+	-	-	-
15.	11.7	M	April	-	-	-	-	-	+	-	+
16.	10.5	F	April	-	-	-	-	+	+	-	+
17.	9.7	M	May	-	-	+	+	+	+	-	-
18.	1.8	M	May	-	+	-	-	-	+	-	-
19.	4.8	M	May	-	-	-	-	-	+	-	-
20.	0.6	M	May	-	-	+	-	+	-	-	-
21.	12.2	F	June	-	-	-	-	-	+	-	+
22.	4.3	M	March	NA	-	-	-	+	+	-	-
23.	16.5	M	April	NA	+	-	-	+	+	-	+
24.	13.7	M	April	NA	-	-	-	+	+	-	+
25.	1.4	M	April	NA	-	-	-	+	-	-	-
26.	1.6	M	May	NA	-	-	-	-	+	-	-

Figure 2. Anti-SARS-CoV-2 seropositivity rate



Source: own compilation. *T1D: type 1 diabetes*

Table 7. Clinical characteristics of children with SARS-CoV-2 testing

Significant differences are highlighted in **bold**. Source: own published paper (226)

T1D: type 1 diabetes, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, COVID+: SARS-CoV-2 seropositive, COVID-: SARS-CoV-2 seronegative

	Newly diagnosed children with serological testing (n=21)			Previously diagnosed children with T1D (n=22)			
	COVID+	*COVID-*	p-value	*COVID+*	*COVID-*	p-value	p-value
SARS-CoV-2 seropositive : seronegative ratio	11:10			5:17			**0.04**
Mean age in years (SD)	8.84 (± 4.63)			10.39 (± 3.46)			0.22
	9.40 (±3.74)	8.07 (±5.51)	0.52	9.92 (±1.70)	10.53 (±3.86)	0.74	
Boy:girl ratio	11:10			12:10			0.89
	3:8	8:2	**0.03**	3:2	9:8	>0.99	
Mean insulin requirements three months after diagnosis in unit/kg (SD)	0.56 (±0.20)	0.43 (±0.18)	0.13				

4.1.3. Autoimmune comorbidities

Newly diagnosed children with T1D admitted during the third wave of the pandemic had a remarkably high rate of autoimmune comorbidities (48.0% had at least one other autoimmune condition besides T1D). The incidence of celiac, thyroid and adrenal autoimmunity in our study group was 26.9%, 24.0% and 7.7%, respectively (see Table 6 and Table 8). The anti-tTG IgA titers measured in seven new T1D patients were highly elevated (median: 3772 U, IQR: 125-27,784 U, range: 98-33,213 U). We compared these results to those diagnosed during the last pre-pandemic year (control group B, n=52). The number of children with at least one new autoimmune comorbidity significantly increased compared to the preceding year before the pandemic (p=0.02). Patients diagnosed in 2021 had a higher rate of celiac autoimmunity compared to those in 2019 (p=0.04). However, the rate of thyroid and adreanal autoimmunity did not differ significantly between the two periods (p=0.11 and p=0.26).

Table 8. The rate of autoimmune comorbidities

Data are presented in ratios and (percentages). Significant differences are marked in **bold**.

	Study group (n=26)	Control group B (n=52)	p-value
Celiac autoimmunity	7/26 (26.9)	4/52 (7.7)	**0.04**
Thyroid autoimmunity	6/25 (24.0)	5/49 (10.2)	0.11
Adrenal autoimmunity	2/26 (7.7)	1/51 (2.0)	0.26
Any autoimmunity	12/25 (48.0)	10/48 (20.8)	**0.02**

4.1.4. Diabetes-specific autoantibodies

All newly diagnosed children with T1D were tested positive for at least one diabetes-specific autoantibody (GAD-65A, IAA, IA-2A, and/or ZnT8A). Individual details are provided in Table 6. The Chi-squared test for trend did not show a significant difference in the number of autoantibodies between the SARS-CoV-2 seropositive and seronegative groups (p=0.11). It is worth drawing attention to the case of a newly diagnosed 7-month-old infant who was affected by maternal COVID-19 infection during pregnancy. At the time of his T1D diagnosis, a high GAD-65A titer (above 2,000) was detected, reinforcing the immunopathological mechanism behind his diabetes, rather than a suspected neonatal diabetes.

4.2. Study II (Thyroid disturbances after COVID-19 and the effect of vaccination in children: a prospective tri-center registry analysis)

4.2.1. Patient characteristics

Between March 24, 2021 and March 23, 2022, we examined 578 children across the three pediatric LC outpatient clinics of Semmelweis University. Finally, a total of 458 children were included in our analysis. The flowchart of patient inclusion can be seen in Figure 1 in the Methods section. Their mean age was 12.4 (± 3.8) years, with 208 (45.4%) being male. Demographic characteristics, method of confirming SARS-CoV-2 infection, and severity of the acute disease are provided in Table 9. Six children had a prior history of a thyroid disorder before contracting SARS-CoV-2. Of these, five exhibited laboratory abnormalities during their initial visit. Detailed information can be found in Table 10.

Table 9. Demographic and epidemiologic characteristics

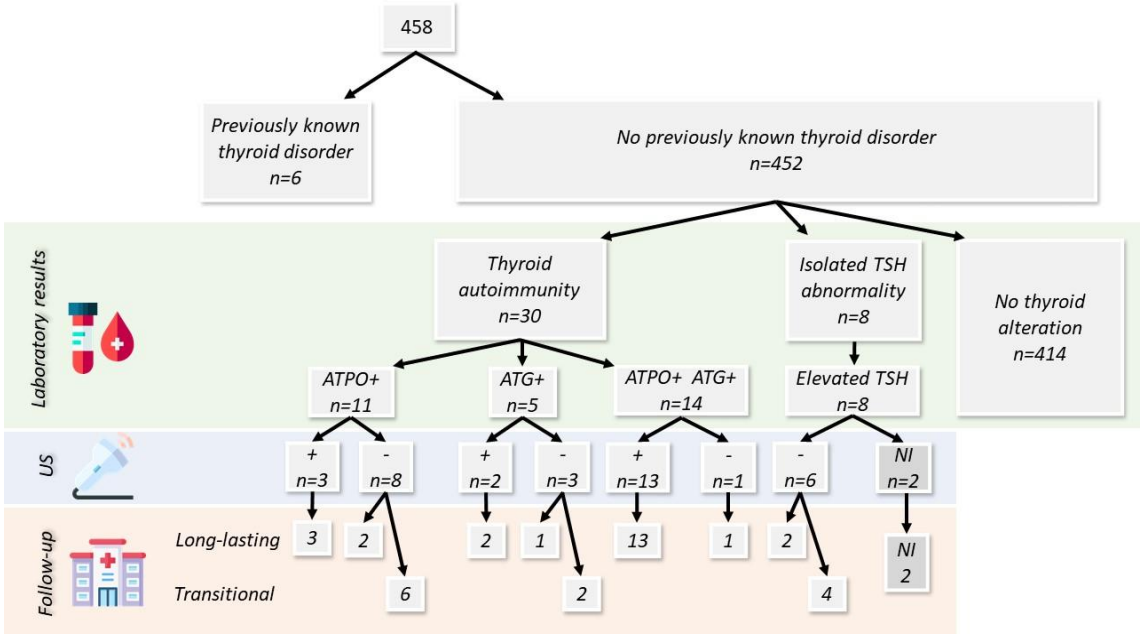
BMI: body mass index, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, PCR: polymerase chain reaction, RAT: rapid antigen test, COVID-19: Coronavirus disease 2019

Characteristics		n (%) / mean (± SD)
Sex		
	Boy	208 (45.4%)
	Girl	250 (54.6%)
Age (years)		12.4 (± 3.8)
Ethnicity		
	Caucasian	457 (99.8%)
	Asian	1 (0.2%)
Height (cm)		154.2 (± 22.1)
Weight (kg)		47.2 (± 18.6)
BMI Z score		0.1 (± 1.2)
Proof of SARS-CoV-2 infection		
	PCR/RAT	290 (63.3%)
	Antibody test	168 (36.7%)
Severity of acute COVID-19		
	Asymptomatic/mild	418 (91.3%)
	Moderate	35 (7.6%)
	Severe	0 (0%)
	Unknown	5 (1.1%)
Positive history of thyroid disease/alterations		
	Yes	6 (1.3%)
	No	452 (98.7%)

4.2.2. Thyroid disturbances at the first evaluation

In the descriptive analysis of thyroid laboratory markers and subsequent comparisons, we excluded the six children with a positive thyroid anamnesis, thus we included 452 children in the final analyses. Among them, 25 had abnormal titers of ATPO and 19 had elevated ATG titers. A total of 30 cases of newly diagnosed TA were identified (6.6%) (see Figure 3. and Table 10.). Isolated TSH abnormalities (all elevated) without autoantibody positivity were observed in eight cases (M = 5.7 mU/L, SD = 0.7 mU/L). Thyroid medication (hormone replacement or anti-thyroid drug) was initiated after the first evaluation in three cases (as shown in Table 10.). Out of 36 ultrasounds performed by pediatric radiologists, 16 were found to be positive (all in children with TA). As a result, the rate of AIT was 3.5% after the first visit.

Figure 3. Flowchart of thyroid laboratory results, ultrasound findings and follow-up



Ultrasound positivity indicates thyroiditis. The ultrasound results include positive findings from both the initial (n = 16) and follow-up examination (n = 2). TSH receptor antibodies are not included in the figure because they were measured (and showed positivity) in only one girl with symptoms suggestive of hyperthyroidism and were not used as a screening test for all children. Source: own published paper (214)

ATPO: anti-thyroid peroxidase, ATG: antithyroglobulin, TSH: thyroid-stimulating hormone, US: ultrasound, NI: no information (missing data)

Table 10. Baseline data of children with thyroid disturbances *(continued on following two pages)*

Non-physiological results are shown in **bold**. Ultrasound changes observed during the follow-up period (n=2) and newly prescribed medications (n=1) are shown in *parentheses* (Neg (Pos) and – (L-thyroxine)). A positive ultrasound meant thyroiditis.

* The patient also had TSH receptor antibody positivity

Source: own published paper (214)

ATPO: anti-thyroid peroxidase, ATG: antithyroglobulin, abs.: absolute value, rel.: relative value, TSH: thyroid-stimulating hormone, fT4: free thyroxine, US: ultrasound, M: male, F: female, Pos: positive, Neg: negative, NI: no information (missing data)

Table 10. Baseline data of children with thyroid disturbances

	Sex	Age (years)	ATPO abs. (U/mL)	ATPO rel.	ATG abs. (UI/mL)	ATG rel.	TSH (mU/L)	fT4 (pmol/L)	Thyroid US	Medication
Children with newly diagnosed thyroid autoimmunity										
1	M	10.8	**229.72**	**41.02**	**194.40**	**1.69**	**5.83**	12.09	**Pos**	-
2	F	10.7	**38.47**	**6.87**	**4004.00**	**34.82**	**9.54**	10.86	**Pos**	L-thyroxine
3	F	8.4	0.16	0.03	**508.60**	**4.42**	3.79		**Pos**	-
4	F	15.5	**29.70**	**5.30**	61.73	0.54	1.06		Neg	-
5	F	6.4	0.16	0.03	**468.20**	**4.07**	1.98		Neg ***(Pos)***	-
6	F	8.4	**77.27**	**13.80**	**258.30**	**2.25**	1.85		**Pos**	-
7	F	14.8	**207.58**	**37.07**	**1121.00**	**9.75**	2.11		**Pos**	-
8	M	12.0	**11.70**	**2.09**	74.05	0.64	2.21		**Pos**	-
9	M	14.5	**135.50**	**24.20**	**371.70**	**3.23**	4.60		**Pos**	-
10	F	13.6	**125.53**	**22.42**	34.41	0.30	1.94		**Pos**	-
11	M	17.6	**5.71**	**1.02**	17.38	0.15	**0.25**	14.48	Neg	-
12*	F	16.1	**3111.10**	**555.55**	**810.50**	**7.05**	**<0.002**	**33.90**	**Pos**	Thiamazole
13	F	15.5	**254.00**	**7.47**	**4000.00**	**34.78**	1.01		**Pos**	-
14	F	13.1	**232.00**	**6.82**	**126.00**	**1.10**	1.63		Neg	-
15	F	11.6	9.03	0.27	**132.00**	**1.15**	0.94		Neg	-
16	M	15.8	**6.00**	**1.07**	13.14	0.11	**0.16**	11.74	Neg	-
17	F	12.9	**8.75**	**1.56**	**187.60**	**1.63**	1.74		**Pos**	-
18	F	5.9	**7.63**	**1.36**	17.59	0.15	2.03		Neg	-
19	F	16.0	0.83	0.15	**229.00**	**1.99**	0.80		Neg	-
20	F	14.3	4.29	0.77	**338.70**	**2.95**	1.36		Neg	-
21	F	14.3	**305.56**	**54.56**	**427.50**	**3.72**	2.81		**Pos**	-
22	F	15.5	**46.80**	**1.38**	**329.00**	**2.86**	0.91		**Pos**	-
23	F	8.3	**817.76**	**146.03**	**344.80**	**3.00**	3.01		**Pos**	- *(L-thyroxine)*
24	F	13.8	**273.83**	**48.90**	**620.20**	**5.39**	**7.86**	13.16	**Pos**	L-thyroxine
25	F	14.3	**193.45**	**34.54**	**586.50**	**5.10**	1.64		Neg ***(Pos)***	-
26	F	13.6	**167.00**	**4.91**	41.20	0.36	1.87		Neg	-
27	F	15.1	**10.13**	**1.81**	31.27	0.27	1.32		Neg	-
28	M	16.8	**6.35**	**1.13**	16.83	0.15	2.48		Neg	-
29	M	14.8	**49.08**	**8.76**	33.14	0.29	1.03		**Pos**	-
30	F	16.5	**11.57**	**2.07**	25.20	0.22	2.85		Neg	-

Table 10. *(cont.)* Baseline data of children with thyroid disturbances

Sex	Age (years)	ATPO abs. (U/mL)	ATPO rel.	ATG abs. (UI/mL)	ATG rel.	TSH (mU/L)	fT4 (pmol/L)	Thyroid US	Medication
Children with newly diagnosed isolated TSH alteration									
31 M	12.1	9.00	0.26	11.60	0.10	**5.08**	13.67	Neg	-
32 M	14.1	0.16	0.03	11.77	0.10	**6.23**	12.51	Neg	-
33 F	15.1	0.16	0.03	17.83	0.16	**5.53**	NI	NI	-
34 F	15.8	1.07	0.19	11.96	0.10	**5.11**	12.08	NI	-
35 M	14.2	1.44	0.26	12.42	0.11	**5.30**	11.84	Neg	-
36 M	9.4	9.00	0.26	11.80	0.10	**5.11**	14.20	Neg	-
37 F	16.1	0.38	0.07	15.21	0.13	**6.45**	14.06	Neg	-
38 M	15.8	0.00	0.00	19.10	0.17	**6.97**	12.98	Neg	-
Children with previously known thyroid abnormality									
39 F	9.5	**92.97**	**16.60**	**489.70**	**4.26**	1.70		**Pos**	-
40 F	17.6	**2381.12**	**425.20**	**387.60**	**3.37**	**8.78**	NI	**Pos**	L-thyroxine
41 F	13.5	**208.57**	**37.24**	24.30	0.21	1.77		**Pos**	-
42 F	17.0	**1380.00**	**40.59**	55.10	0.48	0.76		**Pos**	L-thyroxine
43 M	16.3	9.70	0.29	11.70	0.10	**8.91**	20.00	NI	L-thyroxine

4.2.3. The effect of COVID-19 vaccination

Pathogenic role of vaccination

Eighty-seven children (19.2%) were vaccinated at the time of their first visit (86 with BNT162b2/Pfizer, one with mRNA-1273/Moderna). The association between vaccination and TA was non-significant ($\chi 2(1,N = 452) = 0.138$, $p = 0.815$) (see Table 11). Furthermore, no significant differences were found in relative ATPO ($t(23) = -1.738$, $p = 0.098$) or relative ATG ($t(17) = 0.684$, $p = 0.561$) titers.

Preventive role of vaccination

No children out of the eighteen who had been vaccinated before their acute infection exhibited TA. In contrast, children vaccinated after their infection (n = 52) or who were unvaccinated (n = 365) had a cumulative 7.2% TA rate. As vaccination dates were unavailable for 17 vaccinated children, we excluded them from this analysis. Due to the small sample size, statistical tests were not performed.

Table 11. The impact of vaccination

TA: thyroid autoimmunity, NA: small sample size, values cannot be calculated

		% of TA	χ2	p-value
Pathogenic role	Vaccinated before first visit (n=87)	5.7%	0.14	0.82
	No vaccination before first visit (n=365)	6.8%		
Preventive role	Vaccinated before the acute infection (n=18)	0.0%	NA	NA
	No vaccination before the acute infection (n=417)	7.2%		

4.2.4. Long COVID syndrome and further subgroup analyses

Thyroid autoimmunity and LCS status (LC+ or LC-) showed no significant association ($\chi2(1,N = 452) = 0.342$, $p = 0.321$). The TA group had a higher proportion of girls compared to boys ($\chi2(1,N = 452) = 6.532$, $p = 0.013$, $\Phi = 0.12$). There was no significant association between age (<10 yrs vs. ≥10 yrs) and TA ($\chi2(1,N = 452) = 0.730$, $p = 0.504$) and severity of acute infection ($\chi2(1,N = 447) = 0.262$, $p = 0.490$). (See Table 12). We also examined the rate of 13 symptoms that might suggest thyroid dysfunction. None of them differed between the TA and non-TA groups. (Details can be found in Table 13).

Table 12. Subgroup analyses

Significant differences are highlighted in **bold**.

TA: thyroid autoimmunity, LCS: long COVID syndrome, LC+: children with long COVID syndrome, LC-: children without long COVID syndrome

		% of TA	χ2	p-value
LCS status	LC+	6.1%	0.34	0.32
	LC-	9.1%		
Sex	Girls	9.4%	6.53	**0.01**
	Boys	3.4%		
Age	< 10 years	4.8%	0.73	0.50
	> 10 years	7.2%		
Severity of acute infection	Asymptomatic/mild	6.5%	0.26	0.49
	Moderate	8.8%		

Table 13. The presence of symptoms indicative of thyroid dysfunction in children with and without thyroid autoimmunity

Source: own published paper (214)

Non-TA: children without thyroid autoimmunity. TA: children with thyroid autoimmunity. NA: small sample size, values cannot be calculated, Y: Yes, N: No.

Symptoms		non-TA, % (n)	TA, % (n)	χ^2	p-value	Φ
Fever	Yes	95.2 (40)	4.8 (2)	0.24	1.00	0.02
	No	93.3 (374)	6.7 (27)			
Low fever	Y	97.0 (97)	3.0 (3)	2.67	0.11	0.08
	N	92.4 (316)	7.6 (26)			
Palpitation	Y	92.5 (136)	7.5 (11)	0.31	0.68	0.03
	N	93.9 (277)	6.1 (18)			
Constipation	Y	98.0 (50)	2.0 (1)	NA	NA	NA
	N	92.9 (316)	7.1 (28)			
Diarrhoea	Y	95.0 (96)	5.0 (5)	0.53	0.65	0.04
	N	93.0 (319)	7.0 (24)			
Weight loss	Y	94.3 (99)	5.7 (6)	0.24	0.82	0.02
	N	92.9 (315)	7.1 (24)			
Slowness of movement	Y	94.3 (66)	5.7 (4)	0.09	1.00	0.02
	N	93.3 (348)	6.7 (25)			
Trouble with concentrating	Y	92.0 (173)	8.0 (15)	1.00	0.34	0.05
	N	94.4 (237)	5.6 (14)			
Sleeping less	Y	91.3 (105)	8.7 (10)	1.21	0.28	0.05
	N	94.2 (311)	5.8 (19)			
Sleeping more	Y	94.4 (141)	6.6 (10)	0.00	1.00	0.00
	N	93.5 (274)	6.5 (19)			
Tremors	Y	93.9 (46)	6.1 (3)	0.02	1.00	0.01
	N	93.4 (368)	6.6 (26)			
Persistent fatigue	Y	92.7 (255)	7.3 (20)	0.36	0.70	0.03
	N	94.2 (162)	5.8 (10)			
Hair loss	Y	100.0 (13)	0 (0)	NA	NA	NA
	N	94.9 (74)	5.1 (4)			

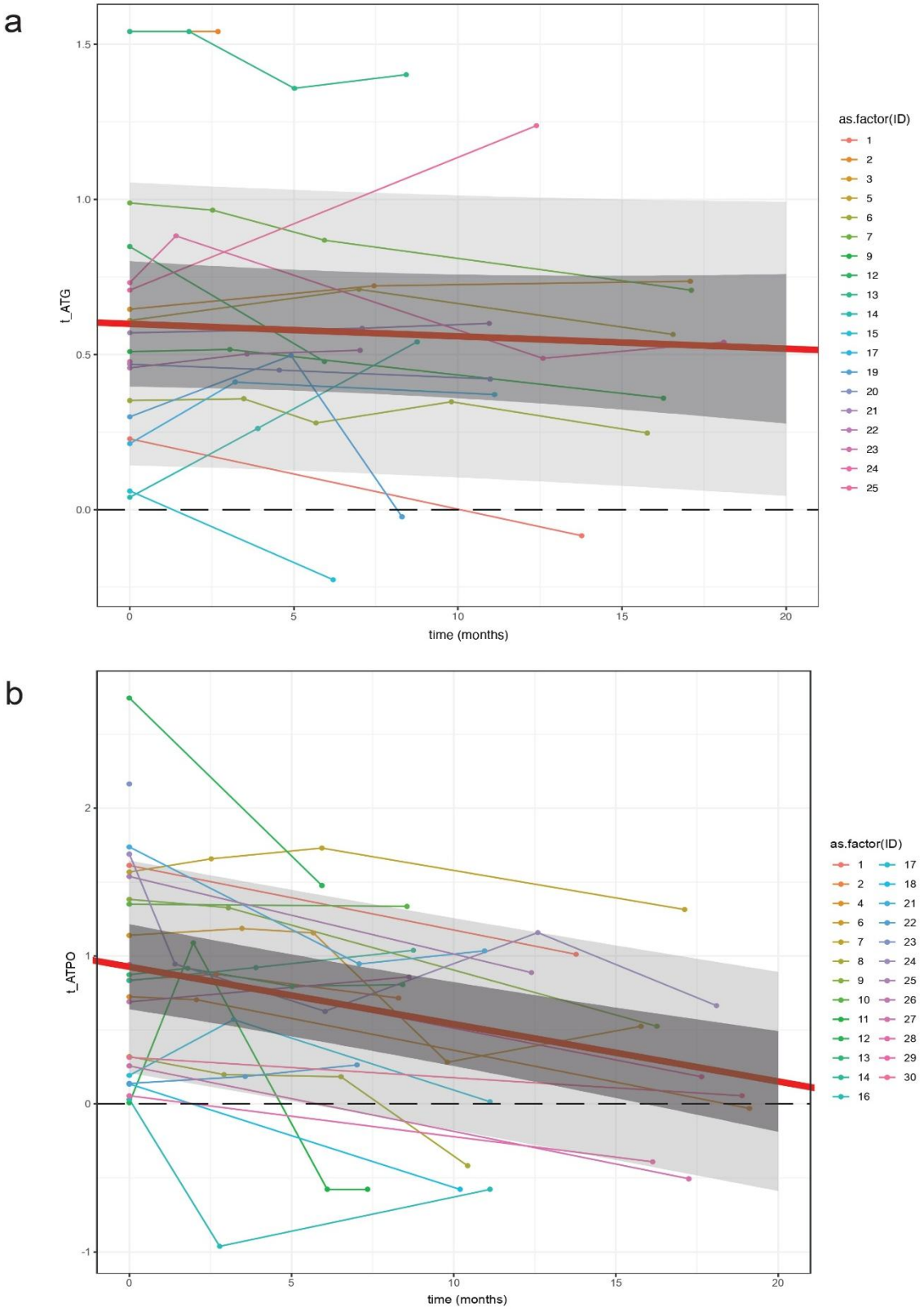
4.2.5. Follow-up assessment

Thirty-six children with newly identified thyroid alterations were followed for a mean of 12.7 (± 4.3) months. Two children were lost to follow-up. Out of the 30 children with TA, 73.3% had long-lasting and 26.7% had transient disturbances. All children who had both ATPO and ATG antibodies and/or a positive ultrasound had long-lasting alterations. Of those with isolated TSH abnormalities (n=8), two had long-lasting, four had transient elevations and two children did not return for follow-up. Details can be seen in Figure 3. Longitudinal changes in relative ATPO and ATG levels are shown in Figure 4a-b. The time effect on ATPO was significant ($\beta = -0.04[-0.05; -0.03]$, $p < 0.001$), showing a decreasing trend, while ATG exhibited no significant change ($\beta = -0.00[-0.01; 0.01]$, $p=0.40$). While no initially positive ultrasound turned into negative, two children with negative baseline ultrasounds developed thyroiditis, increasing the AIT prevalence from 3.5% to 4.0%. Additionally, upon follow-up, we initiated levothyroxine treatment due to new-onset TSH elevation for one girl.

Figure 4a-b. Follow-up of children with initially positive thyroid autoantibodies

a. Antithyroglobulin antibodies (ATG)

b. Anti-thyroid peroxidase antibodies (ATPO)



The numbering represents the same children as in Table 10. Dashed black line: (a) ATG = 1, (t_ATG = log10(1)), (b) ATPO = 1, (t_ATPO = log10(1)). Wide red line: represents the estimated mean effect line, with intervals (inner: confidence, outer: prediction; both are 95% intervals). X-axis: time (months). Y-axis: t_autoantibody = log10(1). Source: own published paper (214)

4.3. Study III (Increasing prevalence of thyroid autoimmunity in childhood type 1 diabetes in the pre-COVID but not during the COVID era)

4.3.1. Patient characteristics

From January 1, 2013 to December 31, 2022, 1,667 patients with insulin-dependent DM received care at our institution. After excluding 14 patients over 21 years of age, 65 children with other forms of diabetes and 227 individuals due to missing data or treatment at other centers, 1,361 children with T1D were included in the final analysis (with 53.2% being male). The mean follow-up was 4.7 (± 2.8) years. Annual demographic data are presented in Table 14.

Table 14. Annual demographic data of included type 1 diabetic children

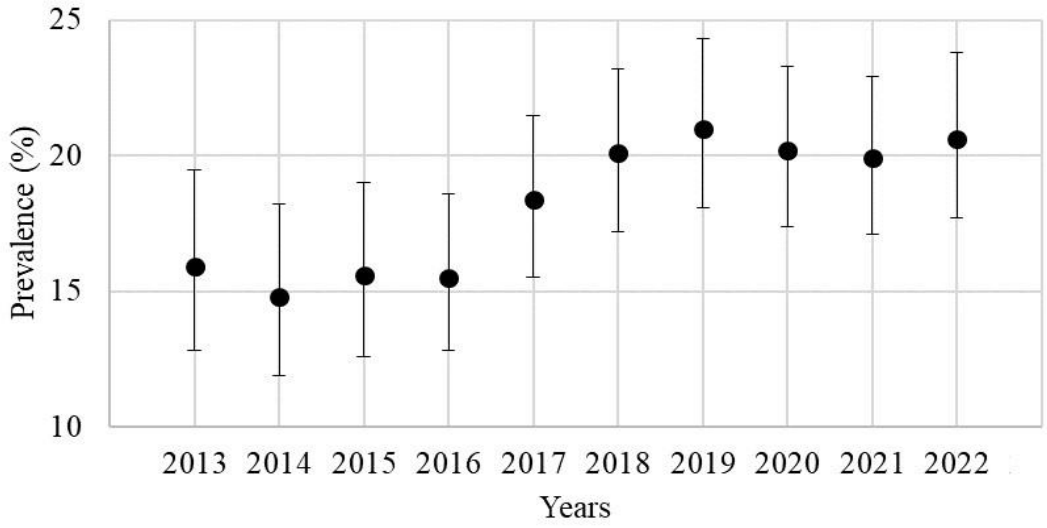
Continuous data are presented as mean (SD). Source: own published paper (225)
T1D: type 1 diabetes

		2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Number of patients		483	513	520	631	680	732	689	738	745	713
Sex	Girls (%)	48.2	46.8	48.5	47.7	46.9	47.4	45.9	47.2	45.9	47.7
	Boys (%)	51.8	53.2	51.5	52.3	53.1	52.6	54.1	52.8	54.1	52.3
Mean age in years (SD)		12.1 (4.1)	12.3 (4.1)	12.5 (3.9)	12.3 (4.1)	12.4 (4.1)	12.4 (4.2)	12.4 (4.1)	12.4 (4.2)	12.5 (4.3)	12.6 (4.3)
Mean time since T1D diagnosis in years (SD)		5.0 (3.8)	5.1 (3.9)	5.3 (3.9)	5.1 (3.9.)	5.2 (3.9)	5.3 (4.0)	5.3 (3.9)	5.4 (3.9)	5.6 (4.1)	5.7 (4.0)

4.3.2. Thyroid autoimmunity and ultrasound-proven thyroiditis

The overall prevalence of TA in our T1D children was 22.8% (95%CI: 20.3;25.5], n=310) with girls being significantly more affected (TA group: 65.8%; non-TA group: 41.2%; p<0.001, RR: 1.60 [95%CI: 1.43;1.78]). From 2013 to 2022, TA prevalence rose from 15.9% to 20.6% (p=0.04), with an increase seen in pre-pandemic years (2013-2019) but not during the COVID-19 era. Annual rates with confidence intervals are presented in Figure 5. Of the 260 children with TA who underwent ultrasound examination, 208 (80.0%, [95%CI: 75.1;84.9]) showed signs of thyroiditis, accounting for 67.1% [95%CI: 61.8;72.4] of all TA cases. As a result, the overall AIT prevalence was 15.3% in our cohort. Among these 208 children, one was later diagnosed with papillary thyroid carcinoma, as was one child without ultrasound signs of thyroiditis. Despite the increasing number of ultrasounds performed over the years, the positivity rate remained stable. Annual rates of ATPO, ATG and ultrasound positivity are shown in Table 15.

Figure 5. Annual prevalence of thyroid autoimmunity



Source: own published paper (225)

Table 15. Annual results of thyroid autoimmunity parameters

Data are presented in percentages and (ratios). Source: own published paper (225)
TA: thyroid autoimmunity, US: ultrasound, ATG: antithyroglobulin, ATPO: anti-thyroid peroxidase

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Prevalence of TA	15.9 (77/ 483)	14.8 (76/ 513)	15.6 (81/ 520)	15.5 (98/ 631)	18.4 (125/ 680)	20.1 (147/ 732)	21.0 (145/ 689)	20.2 (149/ 738)	19.9 (148/ 744)	20.6 (147/ 713)
US positivity rate	81.8 (9/ 11)	82.8 (24/ 29)	85.4 (35/ 41)	82.0 (50/ 61)	88.8 (71/ 80)	79.8 (83/ 104)	75.2 (85/ 113)	79.4 (85/ 107)	83.1 (98/ 118)	83.5 (96/ 115)
Positivity rate of ATG	3.8 (9/ 236)	9.8 (28/ 285)	14.0 (41/ 292)	12.0 (59/ 490)	12.0 (75/ 627)	12.6 (81/ 642)	11.5 (33/ 287)	6.7 (31/ 463)	11.3 (50/ 441)	9.6 (47/ 490)
Positivity rate of ATPO	14.4 (35/ 243)	15.1 (46/ 304)	15.3 (52/ 340)	11.2 (58/ 518)	17.3 (102/ 591)	18.3 (118/ 644)	16.8 (66/ 392)	15.0 (76/ 505)	16.7 (74/ 443)	13.8 (68/ 493)

4.3.3. Thyroid medication requirements

We also aimed to evaluate the rate of thyroid dysfunction among children with TA. As TFTs' levels are influenced by treatment, we analysed thyroid medication data to evaluate the rate of clinically relevant dysfunction. Among the 310 children, seventy-four (23.9%) were treated for hypo- and/or hyperthyroidism: 65 were initially prescribed levothyroxine (including two after thyroidectomy for carcinoma) and nine originally received thyrostatic medications (thiamazole or propylthiouracil). Three children required both types of medication during the study: two transitioned from thiamazole to levothyroxine and one from levothyroxine to thiamazole.

4.3.4. Association between ultrasound positivity and thyroid dysfunction

We assessed the relationship between ultrasound positivity and thyroid function abnormalities in children with at least one ultrasound and one TSH result (n=258). The two previously mentioned children with papillary thyroid carcinoma were excluded as their hormone replacement therapy was a result of thyroidectomy. Children with positive ultrasound results had a significantly higher risk of TSH abnormalities and/or need for

thyroid medication ($p<0.001$, RR: 6.24 [2.05;18.98]). The contingency table with these data can be seen as Table 16.

Table 16. Association between ultrasound findings and thyroid functional abnormalities

Source: own published paper (225)

TSH: Thyroid-stimulating hormone

	TSH Abnormalities/ Medication	No TSH Abnormalities/ Medication	Total number
Positive ultrasound result	76	131	207
Negative ultrasound result	3	48	51
Total number	79	179	258

5. DISCUSSION

5.1. Study I (Anti-SARS-CoV-2 seropositivity among children with newly diagnosed type 1 diabetes mellitus: a case-control study)

During the third wave of the COVID-19 pandemic, we observed an unusually high number of children presenting with newly diagnosed T1D. Based on the growing international literature, we hypothesized that COVID-19 might be linked to the increase seen in new-onset T1D cases. To investigate this potential association, we systematically tested newly diagnosed T1D patients for anti-SARS-CoV-2 spike antibodies. Among those tested, over half (52%) showed serological evidence of prior SARS-CoV-2 infection, significantly higher than the 23% observed in the control group with previously diagnosed T1D.

Several studies have described increased rates of new-onset T1D during the pandemic. (87-89, 227, 228) Yet, it is questionable whether the observed rise shown in these studies simply reflects a pre-existing increasing trend or a natural year-to-year variation in incidence. However, two large studies indicated that the observed T1D incidence was actually higher than what was predicted from data in previous years. (92, 93) In contrast, other studies reported a decline in T1D incidence, though these were mostly conducted during the early phase of the pandemic. (91, 229-231) This temporarily reduced incidence may be explained by the drop in healthcare system utilization during the first wave. (232) Although the clinical onset of T1D cannot remain undiagnosed for long, delayed recognition of symptoms may cause some patients to fall outside the study window and by the time of diagnosis, they may already present with severe metabolic disturbances. This theory is further supported by the increased rates of DKA at presentation reported by numerous studies. (98, 99, 227, 233, 234) Rabbone et al. explain this decreased incidence with reduced exposure to seasonal viral infections due to social distancing. (91)

Our results are in contrast with the findings of three studies that reported similar rates of SARS-CoV-2 seropositivity between newly-diagnosed diabetic children and controls. (114, 115, 235) However, it is important to note that these American, Belgian and Turkish studies were carried out early in the pandemic, whereas our analysis was performed during and after the third wave in Hungary, when a significant rise in pediatric COVID-19 cases was seen. The first comprehensive report that found a connection between prior

SARS-CoV-2 infection and newly diagnosed diabetes was published by the Centers for Disease Control and Prevention (CDC) in January 2022, using data from two major US medical databases. Together, these datasets included over 1.3 million children. However, their data did not distinguish between type 1 and type 2 diabetes. (116) In later years, several other large-scale studies described an increased incidence of T1D after SARS-CoV-2 infection in children (117-119), however, contradictory findings also exsist. (120-122) Pooled analyses of pediatric cohorts have indicated an elevated risk of developing T1D after SARS-CoV-2 infection. (123-125) Rahmati et al. found that this increased risk only existed in studies reporting on US children and adolescents but not in European pediatric populations. (124) While reviewing the literature, it was a question for me whether researchers tend to prefer publishing positive associations, but large, population-based studies helped to minimize the potential impact of publication bias.

Several viruses are hypothesized to trigger autoimmune processes leading to T1D (46, 54, 236) and a similar effect of SARS-CoV-2 cannot be ruled out. Proposed pathophysiological mechanisms include viral persistence, molecular mimicry, bystander activation and epitope spreading. (85, 86, 236) Moreover, experimental studies have demonstrated that the virus can infect β-cells via ACE-2 (the entry receptor for SARS-CoV-2), which is expressed in the pancreas, leading to morphological and functional alterations, such as reduced insulin secretion. (80, 82, 84)

Considering these mechanisms, multiple hypotheses have been proposed to explain the potential connection between SARS-CoV-2 infection and the onset of T1D. These include the possibility that the virus may (1) initiate or accelerate an autoimmune process (indirect effect), (2) act as a final trigger in individuals with ongoing subclinical autoimmunity, resulting in the clinical manifestation of T1D or (3) directly damage pancreatic β-cells, thus inducing diabetes (direct effect). In our cohort, all patients were positive for at least one islet autoantibody, which does not exclude the role of a direct cell-destructive pathway but rather refers to an autoimmune mechanism. Our results are in line with a multicenter study by Kamrath et al., which did not find an increased rate of autoantibody-negative T1D during the pandemic, instead emphasizing an autoimmune pathophysiology. (113)

It is a well-known phenomenon that the seasonal peak in new T1D cases during winter and spring may be linked to the higher incidence of infections during these periods.

(237) The winter season of 2020/2021 was associated with significantly fewer infections, likely due to continuous mask wearing and the closure of public educational institutions. However, the third wave of COVID-19 affected more children, which may have contributed to a non-specific increase in the appearance of new T1D cases. Therefore, the temporal coincidence does not necessarily imply a direct SARS-CoV-2-induced diabetogenic immune response. This is further supported by the observation that the increase in case numbers occurred shortly after the third wave began and the subsequent decline was similarly abrupt (after June 15, 2021, no new cases were recorded for 19 days, compared to the typical three-four new diagnoses per week observed in the preceding weeks).

Based on these findings, we propose that SARS-CoV-2 may either initiate or promote an autoimmune process or, more likely, act as the final trigger that transitions latent autoimmunity into overt clinical T1D (stage 3). Experts from ISPAD also state that the observed rise in incidence may result from concurrent infections triggering the clinical manifestation of T1D, rather than indicating a true increase in disease susceptibility, which typically develops over several years. (21)

During our study period, the rate of autoimmune comorbidities was also high, regardless of whether the child had a history of COVID-19 or not. Several studies reported high rates of TA after SARS-CoV-2 infection; however, as this is the other main focus of this thesis, the relevant literature will be discussed in the following section. Regarding CD, Cakir et al. reported a higher incidence among pediatric patients during the pandemic compared to the pre-pandemic period. (238) However, two other investigations did not observe an increased rate. (239, 240) Moreover, two additional studies that assessed anti-tTG IgA positivity in newly diagnosed T1D cases have found similar rates before and during the pandemic. (195, 196) Still, according to the recently published findings of the Swedish TRIAD study, anti-tTG IgA positivity was associated with SARS-CoV-2 infection in adolescents, but not in younger children. (241)

Strengths

At the time we initiated this study, no published research had directly examined the potential causal relationship between COVID-19 and new-onset T1D; the only available data were the increased incidence rates reported in some studies. Thus, our case-control study provided supporting evidence from a novel perspective.

Limitations

This study is primarily limited by its small sample size and short duration. Data from different waves of the pandemic could have impacted the long-term trends in T1D incidence. In some children, SARS-CoV-2 serological testing could not be performed precisely at the time of diagnosis, instead, it was conducted within a maximum of three months. Therefore, we cannot exclude the possibility that the infection occurred during this timeframe. However, the testing period was similar for both the study and control groups (May-July 2021 vs June-July 2021), suggesting a true difference in seroprevalence between the groups. Another limitation may be the assumption that children with known T1D were more cautious during the pandemic than the general population, potentially resulting in a lower COVID-19 incidence. However, Jia et al. found no significant difference in infection rates between individuals with established T1D and those without diabetes. (114)

5.2. Study II (Thyroid disturbances after COVID-19 and the effect of vaccination in children: a prospective tri-center registry analysis)

In our multicenter prospective analysis of pediatric patients following COVID-19, we diagnosed TA in 6.6% of cases and isolated elevated TSH in an additional 1.8% of them. Autoimmune thyroiditis was identified in 4.0% of the children.

The prevalence of TA in our cohort was higher than that reported in healthy pediatric populations across Europe (4.3% in Finland, 0.6% in Russian Karelia and 3.7% in Spain). (136, 242) However, our findings are similar to those reported in the US, where ATPO positivity was 4.8% and ATG positivity 6.3% in adolescents aged 12-19 years. (243) The prevalence of AIT found in our study is also higher than the 2.5% reported among Greek children. (137) It should be noted that the prevalence of AITD varies greatly across regions due to differences in genetic and environmental factors (e.g. idoine status), therefore these results are not directly comparable. (135, 244)

Voluminous literature exists on AITDs presenting after COVID-19 in adult populations, however, pediatric data remain limited. Regarding thyroid dysfunction, two retrospective analyses reported similar rates in children when comparing the pandemic to the pre-pandemic era. (193, 194) In one of these studies, ATPO titers were assessed only in children with hypothyroidism and no significant change in the rate of ATPO positivity was observed. (193) More lately, a large-scale retrospective observational study utilizing

big data reported a rise in the incidence of both GD and hypothyroidism (including HD) among children in the pandemic period. (165) However, according to the most recently published results of the Swedish TRIAD study, no association was found between SARS-CoV-2 seropositivity and a higher prevalence of TA. (241)

As we do not have control data from children during the pandemic with no history of COVID-19, nor pre-pandemic data from either of these children or the general Hungarian pediatric population, we are unable to draw definitive conclusions about the significance of the TA rate observed in our cohort. It is possible that part of this positivity is attributable to prior SARS-CoV-2 infection, however, it may also simply reflect the baseline prevalence in the general pediatric population in Hungary, with no specific effect of COVID-19.

Since there is a noteworthy hesitancy against COVID-19 vaccines (245), especially when it comes to children, our additional goal was to investigate any vaccination-linked adverse events on the thyroid gland among the youth. One of the main findings of our study was that vaccination against SARS-CoV-2 did not increase the risk of developing TA. The prevalence of TA was similar between children who had been vaccinated prior to their first visit (n=87; 86 with BNT162b2 /Pfizer-BioNTech/, 1 with mRNA-1273 /Moderna/) and those who had not received a vaccine (n=365). Thus, based on our data, a pathogenic role of vaccination in TA development appears unlikely. Although several studies described new-onset GD following various SARS-CoV-2 vaccines (189, 205, 206), a large population-based study also found no increased risk in adults. (210) To the best of our knowledge, our study is the first to examine this issue in the pediatric population.

From another aspect, we aimed to assess the potential protective effect of vaccination by comparing children who were vaccinated before SARS-CoV-2 infection (n=18) with those who were vaccinated after it or remained unvaccinated (n=417). Given the limited sample size, statistical evaluation was not possible, still, it is noteworthy that none of the 18 children vaccinated prior to SARS-CoV-2 infection developed TA in our cohort. Neverthelesss, a large-scale study in adults suggested a potential protective effect of COVID-19 vaccination on the incidence of GD. (212)

To test our hypothesis that TA might be more common in children with LCS (LC+), we compared them to those without persisting symptoms after SARS-CoV-2 infection

(LC-) but found no significant difference in TA prevalence. Thus, our findings suggest that TA is not a contributing factor in pediatric LCS. Subgroup analyses showed TA was more frequent in girls, consistent with substantial previous evidence. (136, 242, 246) However, in contrast to some earlier studies reporting higher TA prevalence in adolescents (136, 242), we found no association with age. Thyroid abnormalities are commonly observed in hospitalized COVID-19 patients (170, 171), yet our data did not demonstrate an association between acute disease severity and the prevalence of subsequent TA. Symptoms of LCS and thyroid dysfunction might overlap. Most children with TA in our cohort had normal fT4 levels and showed no difference in thyroid-related symptoms compared to those without TA. Thus, symptom-based screening alone is insufficient to detect all TA or AIT cases, highlighting the need for comprehensive evaluation.

We considered it important to follow up children with thyroid alterations to assess the persistence of the observed changes. The majority (73%) of those with TA had abnormalities lasting longer than six months. All children with both autoantibody positivity and/or abnormal ultrasound findings showed persistent thyroid alterations. In three cases, progression was observed: two children developed new ultrasound abnormalities and one girl progressed to thyroid dysfunction requiring hormone replacement therapy.

Strengths

To our knowledge, this was the first study to report the prevalence of TA following COVID-19 in a large pediatric cohort. We prospectively evaluated over 450 children for TA and thyroid dysfunction, with systematic data collection on demographics, medical history, acute COVID-19 characteristics, reported symptoms and vaccination status. Moreover, we were the first to examine the potential impact of COVID-19 vaccination on the occurrence of TA in children. Early identification, appropriate management and follow-up of endocrine complications (such as hormonal disturbances and the development of thyroiditis) are essential for preventing long-term consequences, including severe conditions like thyrotoxicosis and the rare but serious case of progression to malignancy.

Limitations

As I described before, the main limitation of this study is the absence of a proper control group comprising COVID-negative children. We initiated a control study during the pandemic (from autumn 2021), but the participants' anti-SARS-CoV-2 antibody results soon revealed that despite their lack of knowledge, most children had already contracted the virus by that time, making it impossible to recruit an appropriate control group. Moreover, pre-pandemic thyroid autoantibody data were missing for these children and surprisingly, no data exist on the prevalence of TA in the general pediatric population in Hungary. It is likely that a substantial proportion of our children already had their thyroid alterations prior to COVID-19, as they showed normal fT4 levels and were thus asymptomatic, therefore no medical evaluation was performed earlier.

Another limitation was the change in the laboratory method used to measure ATPO during the study period. To address this, we calculated and presented relative ATPO values. Although different autoantibody assays can never be perfectly compared, we believe this approach provided a reasonable solution.

5.3. Study III (Increasing prevalence of thyroid autoimmunity in childhood type 1 diabetes in the pre-COVID but not during the COVID era)

In this retrospective analysis of more than 1,300 children and young adults with T1D, we detected an increasing trend in the prevalence of TA during the pre-pandemic years (2013-2020), but not during the pandemic period (2021-2022).

Numerous studies indicate a rising prevalence of autoimmune diseases. (247-249) A population-based cohort study from the United Kingdom (UK) involving 22 million individuals reported the greatest increases in the incidence of CD, Sjögren's syndrome, and GD, however, interestingly, the incidence of HD declined between 2000 and 2019. (250)

In pediatric T1D populations, most studies report pooled prevalence rates of TA. For example, the German/Austrian DPV-Wiss database reported a TA positivity rate of 19.6% (71), while we found an overall prevalence of 22.8%. A recent French study found an overall frequency of 18%, while earlier data from Germany showed a 10-year cumulative incidence of 14%. (251, 252) However, longitudinal trends in TA prevalence among children with T1D remain unexplored.

Although this study initially aimed to assess the pandemic's potential impact on TA prevalence in children with T1D, our findings uncovered a previously underreported tendency: an increasing prevalence of TA prior to the onset of COVID-19. We hypothesized that the high rates of pediatric SARS-CoV-2 infection would lead to an increased TA prevalence among children with T1D during the pandemic, however, our results did not support this preliminary assumption. It should be noted that even if an increase had been observed during the COVID-19 era, our study design could only suggest association, not causality, as multiple pandemic-related and unrelated factors (including the effects of SARS-CoV-2 and COVID-19 vaccination, lifestyle changes, the reduced circulation of other viral infections due to public health restrictions, as well as additional non-pandemic-related causes) may have contributed to any observed trends.

Literature regarding COVID-19 and the subsequent diagnosis of AITD in the general pediatric population has already been discussed in Section 5.2. Therefore, here I will focus on two studies that specifically examined the prevalence of TA in children with T1D. It should be noted that these studies differ from ours in that they examined only children newly diagnosed with T1D each year, whereas we reported the prevalence of TA among all children under our care annually, including both newly diagnosed and follow-up cases. The first study from Turkey reported findings similar to ours, with no significant difference in TA rates among children with new-onset T1D during the first pandemic year compared to the preceding three years. (196) In contrast, the other pediatric report from Kuwait found a risk twice as high of developing TA for those diagnosed before, compared to those who were newly diagnosed with T1D during the three years of the pandemic. Moreover, they observed an association between prior SARS-CoV-2 infection and the presence of thyroid autoantibodies. Unlike our findings, their pre-pandemic data showed a relatively stable TA prevalence. (195)

Our findings are consistent with the voluminous clinical literature describing a female predominance among children with both T1D and TA. (71, 195, 247, 252) Previous research also suggests that older age and longer diabetes duration may elevate the risk of TA. (71, 195) We did not observe this effect in our cohort, as average values for these variables remained stable throughout the study period, minimizing their potential biasing effect on our results.

Although the ISPAD guideline does not require ultrasound for the diagnosis or follow-up of TA, we consider it a positive achievement that the proportion of performed ultrasounds increased more than fivefold during our study period, covering most TA cases by 2022. We believe that ultrasound examination is an essential tool for the early recognition of thyroid malignancies, as demonstrated by two identified cases in our cohort. Importantly, despite this higher rate of performed ultrasounds, positivity rate remained stable over time.

We also assessed thyroid function differences between AIT and TA children. As we expected, children with AIT (those showing ultrasound-confirmed inflammation) had a significantly higher rate of thyroid dysfunction and subsequent medication use than those with TA alone. Notably, three children showed abnormal TSH levels despite lacking ultrasound signs of thyroiditis.

Strengts

The primary strength of our study is the inclusion of over 1,300 children and its 10-year duration, which allowed us to evaluate longitudinal trends in TA prevalence. The year-by-year analysis enabled us to identify patterns more accurately than pooled data would, including the increase observed before the pandemic. Comparing only pre-pandemic and pandemic periods as two groups could have led to a misleading attribution of differences to the pandemic. Since our center provides care for about 25% of all children with T1D in Hungary and is one of the largest in Central Europe, our results are likely representative of the broader region.

Limitations

As a retrospective study, our analysis was limited by occasional missing or incomplete data, often due to missed check-ups, protocol differences among our specialists or inadequate blood samples. Medication-related data was sometimes inconsistently recorded. Finally, it should be highlighted, that autoimmune conditions can present long after infections, therefore, our study period ending in 2022, may not fully reflect the pandemic's long-term effects.

6. CONCLUSIONS

6.1. Study I (Anti-SARS-CoV-2 seropositivity among children with newly diagnosed type 1 diabetes mellitus: a case-control study)

During the third wave of the COVID-19 pandemic, serological testing revealed that more than half of newly diagnosed children with T1D had previously contracted SARS-CoV-2, significantly higher than the 23% in our control group of children with established T1D. These findings suggest that the surge in new T1D diagnoses may be associated with prior SARS-CoV-2 exposure. While a potential role in triggering autoimmunity cannot be excluded (especially in light of the high rate of autoimmune comorbidities observed), given the timing, a nonspecific contribution to disease manifestation also seems reasonable.

6.2. Study II (Thyroid disturbances after COVID-19 and the effect of vaccination in children: a prospective tri-center registry analysis)

Our multicenter prospective study found no evidence that COVID-19 vaccination increases the risk of TA, supporting the safety of the BNT162b2 /Pfizer-BioNTech/ vaccine in this regard. Based on our data, TA does not appear to contribute to LCS in children. The prevalence of TA was higher in girls, but no association was found with age, acute COVID-19 severity or thyroid-related symptoms. The observed prevalence of TA in children with prior COVID-19 was slightly higher than that reported in some European pediatric populations before the pandemic, however, the significance of this finding remains uncertain due to geographical variability. Still, as most abnormalities persisted or even progressed over time, until more data are available, post-COVID thyroid screening and long-term follow-up may be recommended, as they could help in the early detection of endocrine complications. Further experimental and clinical studies are needed to clarify the potential underlying mechanisms.

6.3. Study III (Increasing prevalence of thyroid autoimmunity in childhood type 1 diabetes in the pre-COVID but not during the COVID era)

In our retrospective cohort study, we observed a rising trend in the prevalence of TA among children and young adults with T1D between 2013 and 2022. Interestingly, this increase was evident only before the onset of the COVID-19 pandemic, however, the

incidence appeared to plateau during the pandemic era. Consequently, our findings do not support the involvement of SARS-CoV-2 in the development of TA in this population. Although not required by international guidelines, ultrasound use increased substantially during our study period, enabling near-complete coverage of TA patients by 2022, proving to be valuable for the early detection of malignancies in two cases.

7. SUMMARY

Soon after the onset of the COVID-19 pandemic, research on the long-term effects of SARS-CoV-2 began expanding rapidly. Additionally, from the beginning of 2021, an increasing number of children presented with persistent, debilitating symptoms lasting for months after the acute infection. In response to this new, growing clinical demand, we established the first Pediatric Long COVID Outpatient Clinic in Budapest, Hungary, where we prospectively collected data from children with LC. Concurrently, at our Diabetes-Endocrinology Unit, a sharp rise in new-onset T1D cases was observed.

To investigate pediatric autoimmune endocrinopathies in the context of the COVID-19 pandemic, we conducted three studies.

In a case-control study (Study I), we observed a significantly higher rate of prior SARS-CoV-2 infection among newly diagnosed T1D cases compared to the control group, suggesting a possible (though maybe nonspecific) contribution of COVID-19 to T1D manifestation.

In our prospective multicenter study (Study II), we found no increased risk of TA following COVID-19 vaccination and no association between TA and LC. The observed 6.6% prevalence of TA cannot be interpreted without a proper control group. However, based on the fact that, most abnormalities persisted or progressed, longitudinal follow-up is supported.

To overcome the lack of pre-pandemic control data in Study II, I proposed to select a cohort with regular AITD screening: children with T1D. In this retrospective analysis (Study III), we found no evidence supporting the hypothesized increase in TA prevalence among children with T1D during the pandemic. Instead, we identified a previously underreported trend: a rising prevalence in the pre-pandemic years.

For me, it was truly exciting and inspiring to witness how the scientific process evolved during the COVID-19 pandemic: from initial case reports to increasingly large and controlled studies, eventually arriving at meta-analyses. At first, the vast majority of research focused on adults, but gradually, more and more pediatric studies were published. However, data on children remain limited compared to that in adults (particularly regarding thyroid disorders), highlighting the ongoing need for more pediatric-specific investigations.

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9. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

9.1. Peer-reviewed articles with relevance to the dissertation

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