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Impact of COVID-19 on new-onset type 1 diabetes mellitus – A one-year prospective study

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Abstract. – OBJECTIVE: A positive relationship between the recently emerged Corona Virus Disease-19 (COVID-19) and diabetes has been inferred, but not confirmed, in children. The aim of the present study was to investigate the possible impact of COVID-19 on new-onset Type-1 Diabetes Mellitus (T1DM) in a pediatric population.

PATIENTS AND METHODS: This is a prospective study of all children and adolescents diagnosed with T1DM during the first year of the COVID-19 pandemic (March 2020-February 2021) in Western Greece (population coverage ≈1,000,000). The incidence and severity of T1DM, the age and sex of the participants and HbA1c and c-peptide concentrations at diagnosis were recorded and compared to those of the previous year (pre-COVID-19 year).

RESULTS: 21 children aged 8.03±0.90 years old were diagnosed with T1DM in the COVID-19 year and 17, aged 9.44±3.72 years old, in the pre-COVID-19 year. A different seasonality pattern of new onsets was observed during the COVID-19 year compared to the previous year, with increasing trend from spring to winter (spring: 9.5% *vs.* 23.5%, autumn: 23.8% vs. 29.4%, summer: 19% *vs.* 11.8%, winter: 47.6% *vs.* 35.3%). Also, compared to the preceding year, HbA1c was significantly higher (p=0.012) and the incidence and severity of diabetic ketoacidosis greater (p=0.045, p=0.013, respectively).

CONCLUSIONS: This is the first study to report a different seasonality pattern and increased severity of new-onset T1DM during the first year of the COVID-19 pandemic. Future research should further investigate the possible role of SARS-CoV-2 and the different pattern of overall infection incidence during the COVID-19 year.

Key Words:
COVID-19, Type 1 diabetes mellitus, New onset, Severity, Children.

Introduction

It has been largely described that a genetic component is implicated in the etiology of T1DM, as well as environmental factors, including viral infections that act as triggers for autoimmunity[1]. Involved mechanisms include activation of the immune system causing acute and chronic inflammation of the pancreatic tissue and cross-reactivity of antiviral immune responses and host epitopes, known as molecular mimicry[1]. Viruses that have been implicated in the development of T1DM are HEV[2], rotavirus[3], mumps virus[4], rubella virus[5] and cytomegalovirus[6]. Viral infections and their immunological consequences are considered to contribute to the pathogenesis of Type 1 Diabetes Mellitus by affecting the incidence[7,8] or by changing the seasonal pattern[9]. Besides the role of viruses as inducers or accelerators of T1DM in genetically predisposed patients, evidence exists regarding their protective role against autoimmunity, including T1DM autoimmunity, known as the "hygiene theory". Pathophysiological mechanisms implicated by studies in animal models include reduction in the number of aggressive lymphocytes, which enhances a protective islet environment[10,11]. Stimulation of immunoregulatory CD4 T cells has also been shown to play a central role in several models[12]. All the above suggest a multifaceted relationship between infections and autoimmune diseases and a pivotal role of infection in the induction of autoimmune disorders.

Numerous studies[13-16] have tested the hypothesis that new onset T1DM may display seasonality, however, a consistent pattern has not been established. A global pattern of seasonality of T1DM onset has been suggested, exhibiting winter peaks and summer troughs in many centres[16,17].

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The recently emerged Corona Virus Disease-19 (COVID-19), caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has rapidly spread globally, placing humanity at significant health, socio-economic and psychological risks[18]. It has affected many patients with chronic illnesses as well as patients with diabetes mellitus. In adults, the prevalence of subjects with diabetes affected by COVID-19 does not differ from the prevalence of diabetes in the general population[19,20]. However, in hospitalized adults with COVID-19 a positive association has been described between diabetes and severe disease or mortality rates. This is possibly due to the pre-existence of micro- and macrovascular complications[21]. In a large UK study (OpenSAFELY) of 10,926 COVID-19 deaths, greater mortality occurred with poorer glycemic control[22]. Patients with diabetes with HbA1c >7.5% showed increased mortality risk compared to those with HbA1c<7.5%. The same findings were demonstrated by the NHS England study in both patients with T1DM and type 2 diabetes mellitus. COVID-19 has also been shown to induce hyperglycemia in patients without diabetes, secondary to infection, which increases the risk of critical disease[23,24].

In children and adolescents there are less data on whether SARS-CoV-2 has an impact on the incidence, seasonality and severity of the newly diagnosed T1DM children. In a German study no strong short-term influence of the COVID-19 pandemic on T1DM incidence was established[25]. However, in this study the aim was to investigate the influence of the German lockdown on T1DM incidence, which was for only 2 months. Therefore, any impact of the COVID-19 pandemic on the T1DM incidence and possible changes in seasonal variation cannot be assessed for this short period of time. Another study[26] from the US and Canada, of 48 patients aged 0-21 years old that were admitted to the PICU due to COVID-19, 8% had diabetes. However, other studies failed to confirm a positive relationship between diabetes and severe disease in children[27]. Due to the small number of relative studies, the impact of COVID-19 on T1DM in children and adolescents remains obscure.

The aim of the present study was to study the impact of the COVID-19 pandemic on epidemiological indicators of new onset T1DM, such as the incidence, seasonality and severity, in children and adolescents from Western Greece. For this purpose, the age, sex, the total incidence, timing and severity of new T1DM diagnoses were studied in a large pediatric population from the 4th in size administrative region in Greece and compared to those of the preceding year. Epidemiological data regarding the confirmed COVID-19 cases in the country were taken into consideration.

Patients and Methods

This is a prospective study of the new-onset T1DM cases in Western Greece during the first year of the COVID-19 pandemic (COVID-19 year: March 2020 to February 2021). All children and adolescents aged less than 18 years old who were diagnosed with T1DM and/or diabetic ketoacidosis (DKA) at the University General Hospital of Patras and the Karamandaneion Children's Hospital of Patras were recruited. The two hospitals provide tertiary services for the geographical area of the Region of Western Greece (population coverage ≈1,000,000). All patients presenting with DKA or diagnosed with T1DM in this area are referred to and managed at these hospitals.

The overall incidence of new cases of T1DM or DKAs, the severity of DKA, the need for admission to the pediatric intensive care unit (PICU), and the monthly and seasonal distribution of the diagnoses, were recorded. Also, the age of the participants, the HbA1c and c-peptide concentrations on admission, as well as the duration of diabetes-related symptoms prior to admission, as reported by the parents, were assessed. All the studied parameters were also retrospectively collected for the preceding 12-month period (pre-COVID-19 year: March 2019-February 2020) and compared to those of the COVID-19 year. All patients who were diagnosed with T1DM during the COVID-19 year were tested negative for SARS-CoV-2 on admission to the pediatric ward.

DKA was categorized into three groups based on severity: mild (blood gas pH: 7.2-7.3 and/or HCO_3^-: 10-15 mmol/L), moderate (pH: 7.1-7.2 and/or HCO_3^-: 5-10 mmol/L) and severe (pH<7.1 and/or HCO_3^-<5 mmol/L).

The study was approved by the Research Ethics Committee of the University General Hospital of Patras (IRB: 129/10.3.2012) and is in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983. Written informed consent was obtained from the parents of the participants.

Statistical Analysis

Collected data from the medical record, along with demographic information were analyzed with the use of the software IBM SPSS Statistics 22 for windows (SPSS, Chicago, IL, USA). Continuous variables are presented as a mean ± standard deviation (SD). To evaluate the effect of independent variables on dependent variables, the analysis of variance (ANOVA) was used. The Mann-Whitney test was used in order to compare the non-normality parameters and Pearson's correlation was used to evaluate the relation between quantitative variables. The threshold for statistical significance was defined as $p \leq 0.05$.

Results

In total, 21 children and adolescents were diagnosed with T1DM and/or DKA during the COVID-19 year, and 17 the year before. All the children and adolescents diagnosed during the pre-COVID-19 year were symptomatic and developed either ketosis or ketoacidosis prior to diagnosis. Among the children and adolescents diagnosed during the COVID-19 year, 18 were symptomatic prior to diagnosis and presented either with ketosis or ketoacidosis. Three were asymptomatic and were coincidentally diagnosed with hyperglycemia during routine check-up. The age, sex, HbA1c levels, c-peptide concentrations, duration of symptoms, the incidence and severity of ketoacidosis, admission to the PICU and the season of diagnosis of children and adolescents diagnosed with T1DM during the pre-COVID-19 and COVID-19 years are shown in Table I. The same parameters when patients with coincidental diagnosis of T1DM were omitted are also shown in Table I.

No statistically significant differences were found in the age and sex of children and adolescents diagnosed with T1DM between the two studied years. When children were categorized by age, 33.3% of those diagnosed during the COVID-19 year were below 6 years of age, 52.4% were between 6 and 12 years old and 14.3% were above 12 years old. The corresponding percentages during the pre-COVID-19 year were 17.7%, 64.7% and 17.6%, respectively (p=0.105).

Seasonal distribution of T1DM diagnoses showed that during the COVID-19 year, the incidence of new diagnoses of T1DM were low during spring and increased gradually during the summer, and, subsequently, autumn and winter (Table I). Comparison with the pre-COVID-19 year showed a lower rate of new diagnoses of T1DM in the COVID-19 year during spring and autumn and a higher rate during the summer and, particularly, during winter (Table I). The monthly and seasonal distributions of the new diagnoses are shown in Figures 1 and 2.

HbA1c concentrations had a tendency to be higher in patients diagnosed during the COVID-19 year compared to the pre-COVID-19 year but did

Table I. Characteristics of children and adolescents diagnosed with T1DM during the COVID-19 year and pre-COVID-19 year.

Characteristics	Pre-Covid-19 year N = 17	Covid-19 year N = 21	Covid-19 year (symptomatic)* N = 18	*p*-value	*p*-value*
Age (years)	9.44 (± 3,72)	8.03 (± 0.90)	7.90 (± 4.3)	0.442	0.318
Gender	70.6% (male)	42.9% (male)	44.4% (male)	0.092	0.187
	29.4% (female)	57.1% (female)	55.6% (female)		
HbA1c (%)	10.94 (± 0.27)	12.07 (± 0.52)	12.67 (± 1,92)	0.080	0.012
C-peptide (ng/ml)	0.9 (± 0.12)	0.69 (± 0.12)	0.66 (± 0,44)	0.136	0.083
Duration of Symptoms (months)	1.56 (± 0.38)	–	0.90 (± 0,68)	–	0.257
Ketoacidosis	35.3%	66.7%	77.8%	0.045	0.019
Only ketosis	93.3%	81.1%	83.3%	0.547	0.736
PICU	5.9%	28.6 %	33.3%	0.076	0.044
Severity of DKA	83.3% (mild)	14.3% (mild)	14.3% (mild)	0.013	0.013
	0% (moderate)	21.4% (moderate)	21.4 (moderate)		
	16.7 (severe)	64.3% (severe)	64.3% (severe)		
Season	23.5% (spring)	9.5% (spring)	11.1% (spring)	0.620	0.508
	11.8% (summer)	19% (summer)	16.7% (summer)		
	29.4% (autumn)	23.8% (autumn)	22.2% (autumn)		
	35.3% (winter)	47.6% (winter)	50% (winter)		

Values are presented as mean ± SD. *Symptomatic children and adolescents. Coincidentally diagnosed asymptomatic children and adolescents (without ketosis/ketoacidosis) were omitted.

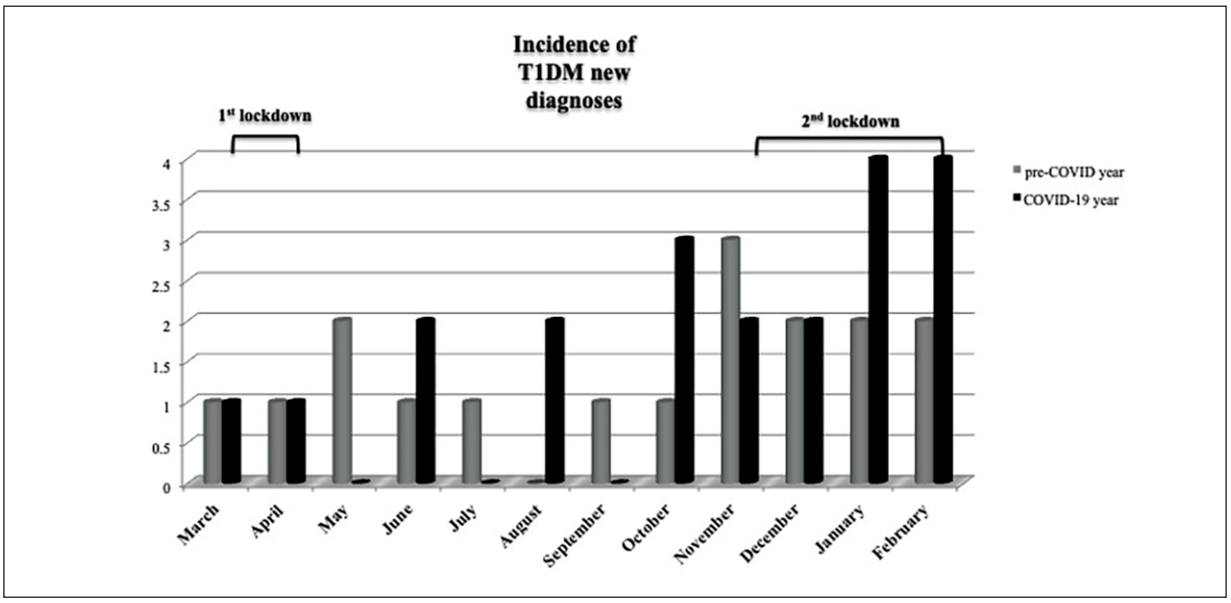

Figure 1. Monthly distribution of new cases of T1DM during the COVID-19 year and the pre-COVID-19 year.

not reach statistical significance (p=0.08). When the patients coincidentally diagnosed with T1DM during routine checkup (asymptomatic, no ketosis/ketoacidosis) in the COVID-19 year were omitted, the difference in the HbA1c concentrations reached statistical significance (p=0.012) between the two years (Table I). The c-peptide concentrations were similar in the two groups (p=0.136) even when asymptomatic patients during COVID-19 year were omitted (p=0.083) (Table I).

Duration of diabetes-related symptoms prior to T1DM diagnosis was not significantly different in patients diagnosed during and prior to the COVID-19 year (p=0.257). However, the rate and severity of DKAs was significantly increased during the COVID-19 year compared to the pre-COVID-19 year, (p=0.045 and p=0.013, respectively), as well the admissions to PICU (p=0.044) (Table I).

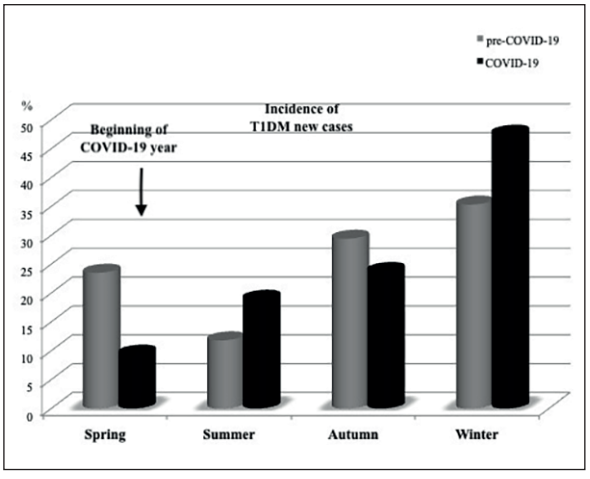

Figure 2. Seasonal distribution of new cases of T1DM during the COVID-19 year and the pre-COVID-19 year.

Discussion

Our study shows that the incidence of new onset T1DM in children and adolescents during the COVID-19 year was not increased compared to that of the previous year, as opposed to the distribution throughout the year, which varied significantly. The number of cases diagnosed exhibited a gradually increasing trend from the outbreak of the pandemic (March 2020) to the end of the following 12 months. In the pre-COVID-19 year there was a decline in the number of cases diagnosed in the summer compared to those diagnosed in the spring, and an increase again in the autumn and winter (Figure 2). This is in consistency with the global pattern of seasonality described by several studies[16,17]. The same seasonal distribution was observed during the 6 years prior to the COVID-19 outbreak in the same area, when data from a study conducted by our group throughout the 5-year period 2014-2018 were added to our pre-COVID-19-year data[16] (Figure 3).

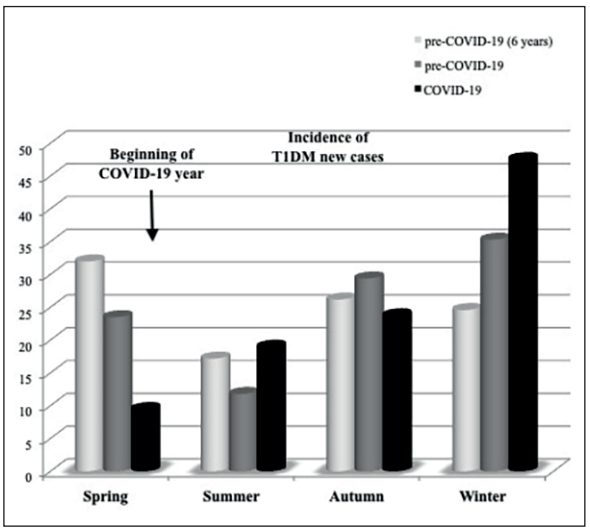

Figure 3. Seasonal distribution of new cases of T1DM during the COVID-19 year, the pre-COVID-19 year and the 6-year period prior to the COVID-19 year.

All data indicate a delayed presentation of new T1DM cases after the COVID-19 outbreak. Possible explanations include restricted overall transmission of infections during the first months of the COVID-19 pandemic due to the application of preventive and self-hygiene measures. Several studies[28-30] have shown a sharp reduction in the rate of ED visits in children and adults during the first phase of the pandemic. Our team has reported a decline, by approximately 60%, in the ED visits and overall infection rate in the same area of Western Greece after the COVID-19 outbreak[31]. The decline was apparent throughout the whole COVID-19 year, particularly though during the first pandemic wave and lockdown period (March-April) and the months immediately after, supposedly due to the application of confinement measures and social distancing. Infections and autoimmune diseases are known to have a multidirectional relationship and viral agents are thought to be able to modulate the immune system[32,33]. Hence, a possible explanation of the delayed presentation of new T1DM cases in the COVID-19 year could hypothetically involve a switch of the immune system towards autoimmunity due to the absence of infectious triggers and the significant reduction in the overall infection rate at the early stages of the pandemic.

However, alternative explanations may also be hypothesized. After the first pandemic wave, control measures were officially relaxed and, additionally, with progression of time people showed signs of fatigue and reduced compliance to protective measures. As a result, the overall infection rate begun to increase gradually from May to October 2020. We speculate that it may have acted as a trigger to development of T1DM on genetically susceptible children and adolescents. We also hypothesize that some of the new cases of T1DM that would expectedly have been triggered by an infectious factor during the first phase of the pandemic may have presented later, when infectious triggering actually occurred.

In addition to the overall infection rate noted to be rising after the first few months of the pandemic, SARS-CoV-2 infection also exhibited a sharply rising prevalence in the country (**Supplementary Figure 1**). Theoretically, the increase in the new cases of T1DM could have been caused in part by this virus. However, there was no evidence of COVID-19 infection at the time of diagnosis in any of the patients. All were tested negative for SARS-CoV-2 on admission to the pediatric ward and no positive current or recent history of infection-related symptoms was reported to any of the patients or their families. However, it is possible that some of the patients might have experienced a subclinical course of the COVID-19 or might have ignored mild symptoms, which might have triggered the onset of T1DM in those genetically susceptible. The possible implication of SARS-CoV-2 in the different pattern of new T1DM diagnoses during the COVID-19 year was investigated through serology testing for SARS-CoV-2 antibodies that could confirm recent or previous COVID-19 infection. However, testing for SARS-CoV-2 antibodies in 60% of the newly diagnosed T1DM patients revealed that 90% were negative, thus, these results do not support a strong impact of SARS-CoV-2 on new-onset T1DM.

Furthermore, accumulated anxiety and psychological distress with progression of time due to the significant changes in lifestyle should not be ignored since it is a well-established causative factor of immune dysregulation[25]. Historically, infectious disease outbreaks have a psychological impact on societies[34] and the same has been shown for the COVID-19 pandemic[35,36]. Moreover, increased incidence of T1DM has been observed after stressful catastrophic events, such as the Chernobyl incident in 1986 and the Los Angeles earthquake in 1994[37,38].

Our data also suggest a potentially more aggressive evolution of T1DM during the COVID-19 year compared to the previous year.

This is supported by the significantly higher HbA1c levels at diagnosis and a decrease by 42% in duration of diabetes-related symptoms compared to the previous year. Another finding in line with the above-mentioned data suggesting a more aggressive course of T1DM development during the COVID-19 year is the significant higher incidence and severity of ketoacidosis leading also to a higher admission rate to PICU. Similarly, a study[39] from the Italian Society for Pediatric Endocrinology and Diabetes (ISPED) for the early phase of the pandemic, reported that although the new onsets of T1DM were less than those in the same period one year before, DKAs were more severe. Thus far, our data are the only available regarding the incidence of T1DM throughout the whole year post the outbreak of the pandemic.

The present study has some strengths and limitations. Among the strengths is the fact that this is the first study worldwide to investigate the incidence, severity, monthly and seasonal variation of newly diagnosed T1DM cases during the first year after the COVID-19 outbreak and to compare them to those of the previous year. This is also the first study to report a different pattern of yearly distribution of the diagnoses. This infers a potential causative role of the low overall infection rate during the first phase of the pandemic, followed by the increased overall infection rate and infection rate by SARS-CoV-2 later. Regarding limitations, the possible role of SARS-CoV-2 in the induction of T1DM on its own accord cannot be confirmed due to the restricted number of patients who had serology SARS-CoV-2 testing and due to the smallness of the studied sample. Further studies are needed to clarify whether psychological aspects, increased infection rate following an initial absence of viral triggers, the effect of prolonged lockdown of the society, or other factors play a causative role in the observed seasonal incidence shift and severity of new onset T1DM.

Conclusions

This prospective study is the longest worldwide to investigate the possible impact of the COVID-19 pandemic on epidemiological indexes of new onset T1DM in children and adolescents. We observed a different pattern of presentation of newly diagnosed T1DM cases following a different pattern of infection incidence, as well as increased severity of the new presentations of T1DM. Our findings should prompt further research in larger populations and for longer periods in order to address the emerging questions.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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