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## **THE IMPACT OF THE COVID-19 PANDEMIC ON THE INCIDENCE OF TYPE 1 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS IN THE GENERAL HOSPITAL "DR. LAZA K. LAZAREVIĆ", ŠABAC**

**Abstract:** *Introduction and Objectives:* Over the past few years, a surge in the incidence of Type 1 Diabetes Mellitus (T1DM) has been observed worldwide, especially during the COVID-19 pandemic. The aim of our research is to shed light on the incidence of Type 1 Diabetes Mellitus in children and adolescents at General Hospital "Dr. Laza K. Lazarević" in Šabac, as well as the impact of the COVID-19 pandemic. *Methodology:* General Hospital "Dr. Laza K. Lazarević" in Šabac serves a population of 35,141 children aged 0–19 years from the Mačva District territory. Data were collected through a retrospective analysis of electronic medical records of children and adolescents diagnosed with T1DM at General Hospital "Dr. Laza K. Lazarević" in Šabac from January 2013 to December 2022. *Results:* Throughout this ten-year period, the average incidence of Type 1 Diabetes Mellitus in children under 19 was 14.80 per 100,000, with the highest incidence found in the group aged 10–14 years and the lowest incidence found in the group aged 15–19 years. During the years of the COVID-19 pandemic, a slightly higher incidence was recorded compared to the years before the pandemic, although the difference was not statistically significant. *Conclusion:* Based on the data from our study, it is clear that the COVID-19 pandemic has had some impact on the occurrence of Type 1 Diabetes Mellitus in children, as it is associated with a higher incidence of T1DM compared to the years preceding the COVID-19 pandemic.

**Keywords:** Type 1 Diabetes, Children, Incidence, COVID-19

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## ***Introduction***

Type 1 diabetes mellitus (T1DM) is the result of the interaction of genetic, environmental, and immunological factors, which ultimately lead to the destruction of pancreatic beta cells and subsequent insulin deficiency. It represents the most common type of diabetes occurring in children and adolescents. Due to infection or exposure to external stimuli, an autoimmune process is initiated, causing a reduction in the mass of beta cells, and insulin secretion becomes disturbed. It is believed that in these affected individuals, insulin deficiency develops over months and/or years, making them more susceptible to the development of ketoacidosis [1]. The incidence of T1DM worldwide is increasing at the rate of 3–4% annually for unclear reasons, particularly during the COVID-19 pandemic [2].

The aim of our research is to present the incidence of T1DM in General Hospital “Dr Laza K. Lazarević” in Šabac and explore the impact of the COVID-19 pandemic.

## ***Methodology***

Data were collected through a retrospective analysis of electronic medical records of children and adolescents diagnosed with T1DM at General Hospital “Dr Laza K. Lazarević” in Šabac from January 2013 to December 2022. Diagnoses were made based on the guidelines from the International Society for Pediatric and Adolescent Diabetes (ISPAD) [3]. All children and adolescents were then referred to tertiary healthcare institutions — either the Mother and Child Health Care Institute “Dr Vukan Čupić” in Belgrade (IMD) or the University Children’s Hospital in Belgrade (UDK) — where the diagnosis was confirmed. The set of the analyzed data consists of the patients’ sex, age at the time of diagnosis, date of diagnosis, presence of diabetic ketoacidosis (DKA), and for patients diagnosed after 2020, any evidence of the presence of acute COVID-19 infections with the COVID-19 virus based on SARS-CoV-2 Rapid Antigen Test and on the history of prior infection or contact with COVID-19 patients. The presence of DKA at the time of diagnosis was determined based on blood glucose levels  $> 11$  mmol/L (200mg/dL) coupled with a venous pH  $< 7.3$ , or bicarbonate levels  $< 15$  mmol/L, alongside the presence of ketonemia or ketonuria. Patients were divided into five age groups: 0–4 years, 5–9 years, 10–14 years, and 15–19 years. General Hospital “Dr. Laza K. Lazarević” in Šabac serves the children from Mačva District territory, including municipalities of Šabac, Koceljeva, Vladimirci, and Bogatić. According to the 2011 National Census, there were 35,141 children aged 0–19 in this territory: 23,360 in the Šabac municipality; 2,567 in Koceljeva; 3,298 in Vladimirci; and 5,916 in Bogatić. These figures were used to calculate the incidence of T1DM from January 2013 to December 2022.

**Statistics**

The statistical analysis used both descriptive and analytical statistical methods. All statistical analyses were performed using the SPSS software package, version 23. Significance was defined as for the level  $p < 0.05$ . The results are presented in both tabular and graphic formats.

The Ethics Committee of General Hospital “Dr Laza K. Lazarević” in Šabac granted approval for the research to be conducted.

**Results**

During this ten-year period, 52 patients aged 0–19 were identified with newly diagnosed Type 1 Diabetes Mellitus (T1DM), with an average ten-year incidence rate of 14.80 per 100,000 (Figure 1, Table 1).

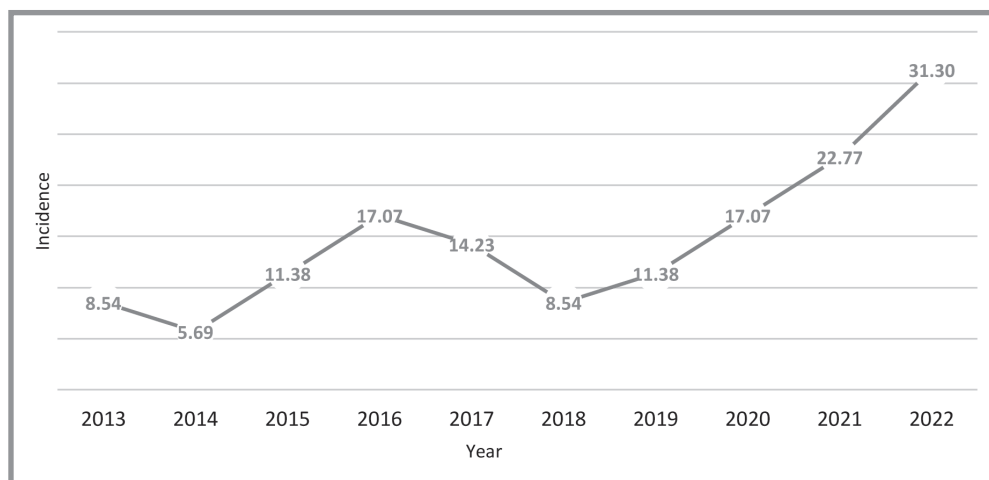


Figure 1. T1DM Incidence in the Mačva District, in the period 2013–2022

**Table1. T1DM Incidence by Municipality in the Mačva District**

		2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total
Municipality Šabac	number	3	1	2	5	2	3	3	4	6	9	38
	incidence	12.84	4.28	8.56	21.40	8.56	12.84	12.84	17.12	25.68	38.53	162.67
Municipality Koceljeva	number	0	0	1	0	2	0	0	1	1	1	6
	incidence	0	0	38.96	0	77.91	0	0	38.96	38.96	38.96	233.74
Municipality Vladimirci	number	0	1	1	1	0	0	0	1	0	1	5
	incidence	0	30.32	30.32	30.32	0	0	0	30.32	0	30.32	151.61

		2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total
Municipality Bogatić	number	0	0	0	0	1	0	1	0	1	0	3
	incidence	0	0	0	0	16.90	0	16.90	0	16.90	0	50.71
Mačva District	number	3	2	4	6	5	3	4	6	8	11	52
	incidence	8.54	5.69	11.38	17.07	14.23	8.54	11.38	17.07	22.7	31.30	147.98 (14.80*)

\* Average ten-year T1DM incidence per 100,000

Of the total 52 patients, 29 were male (55.8%), and 23 were female (44.2%) (Table 2). Statistical analysis of the data did not reveal a statistically significant difference in the occurrence of T1DM based on gender ( $\chi^2$  test;  $p=0.539$ ).

**Table 2. T1DM Incidence in children of different sex**

Sex	Male	Female	Total	p
Number	29	23	52	0.539
%	55.8%	44.2	100	
Population	18,332	16,809	35,141	
Average incidence	15.82	13.86	14.80	

The highest incidence was observed in the age group of 10–14 years, while the lowest was observed in the age group of 15–19 years (Table 3).

**Table 3. T1DM incidence in children by age groups in Mačva District in the period 2013–2022**

Age group	0–4 years	5–9 years	10–14 years	15–19 years
Number	9	16	20	7
%	17.3	30.8	38.5	13.5
Population	7,714	8,858	8,620	9,949
Average incidence	11.67	18.06	23.20	7.03

The number of newly diagnosed cases for each month of the year exhibited a seasonal distribution, with the lowest incidence occurring from June to October (Figure 2).

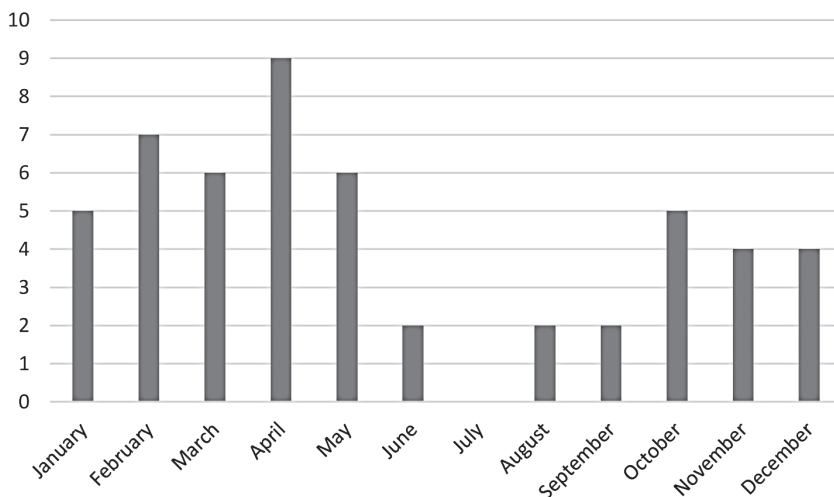


Figure 2. Seasonal distribution of T1DM in children aged 0–19 years

In the period between 2020 and 2022, during the COVID-19 pandemic, the number of newly diagnosed cases was 25/52 (48.1%). Of these, 1 out of 25 patients (4.0%) had recovered from a COVID-19 infection, while 1 out of 25 patients (4.0%) had an acute infection, and 5 out of 25 patients (20.0%) had been in contact with someone who had COVID-19.

Statistical analysis revealed no significant difference in the incidence of T1DM before the COVID-19 pandemic (2013–2019) and during the pandemic (2020–2022) (chi-squared test:  $p=0.782$ ) (Figure 3).

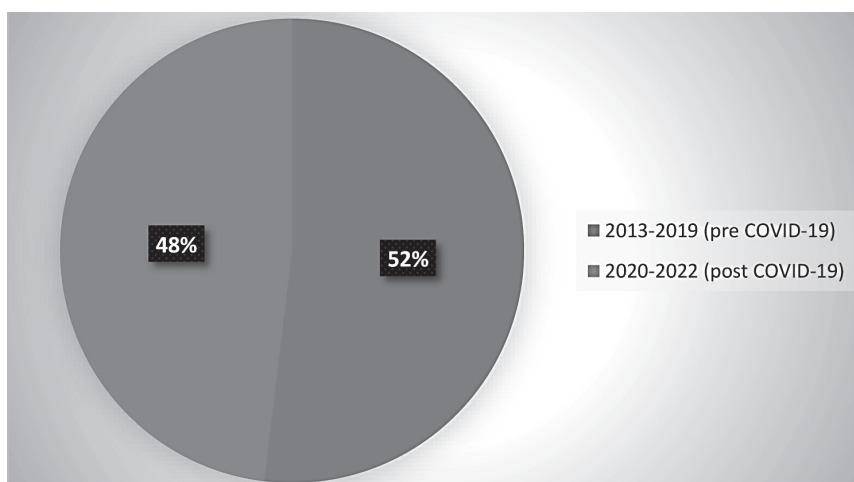


Figure 3. T1DM incidence before and during the COVID-19 pandemic

At the time of diagnosis, 13 out of 52 (25%) patients with newly diagnosed T1DM were in diabetic ketoacidosis (DKA); 39 out of 52 (75%) were in a compensated state. Before the COVID-19 pandemic, 7 out of 27 (25.9%) children were in DKA at the time of diagnosis; during the COVID-19 pandemic, 6 out of 25 (24%) patients were in DKA at the time of diagnosis. No statistically significant difference was observed in the proportion of children presenting in DKA at the time of diagnosis when comparing the periods before the COVID-19 pandemic (2013–2019) and during the COVID-19 pandemic (2020–2022) (Pearson  $\chi^2$  test;  $p=0.873$ ).

## ***Discussion***

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia, caused by a deficiency or dysfunction of insulin. It can be divided into four general categories: 1. Type 1 Diabetes, 2. Type 2 diabetes, 3. Specific Types of Diabetes, and 4. Gestational Diabetes [1].

Type 1 diabetes mellitus (T1DM) typically occurs during childhood and adolescence, but it can also develop at any point in life. It most commonly results from autoimmune destruction of the pancreatic  $\beta$ -cells triggered by environmental factors in genetically predisposed individuals. The disease progresses through four stages, driven by chronic autoimmune destruction of the  $\beta$ -cells in the pancreas, leading first to partial and then complete insulin deficiency. Symptoms manifest when almost 90% of the pancreatic  $\beta$ -cells are destroyed. Children typically present with classic symptoms of T1DM, including polyuria, polydipsia, polyphagia, and weight loss, although the first manifestation of the disease can also be symptoms and signs of diabetic ketoacidosis in the form of severe dehydration and deep, labored breathing. Diabetic ketoacidosis is a life-threatening condition that requires timely recognition and initiation of treatment [1, 3].

In addition to genetic factors, environmental factors (infectious, nutritional, chemical, etc.) also play an important role in the pathogenesis of T1DM, specifically in the development of autoimmunity [3]. Given that viral infections (primarily enteroviruses) are considered one of the most significant potential triggers for the disease in genetically predisposed individuals [2], and considering the observed increase in the number of children with newly diagnosed T1DM during the COVID-19 pandemic, some authors believe that SARS-CoV-2 could in a similar manner have the potential to trigger the disease [4, 5, 6].

The incidence of Type 1 Diabetes Mellitus (T1DM) is globally on the rise worldwide, but the rates vary significantly depending on geographic region, the country's economic standard, and age. A significant increase in the incidence of T1DM has been observed in some regions such as Australia, North America, and Europe, and the incidence is significantly higher in countries with a high economic

standard (7.89/100,000), as well as in children aged 10–14 years (18.02/100,000) [2].

Serbia belongs to the group of countries with a high incidence (11.82/100,000) [7] and prevalence (135.25/100,000) [8] of T1DM in children and adolescents. Moreover, there has been a noticeable rise in the T1DM incidence in children and adolescents [7, 9] in recent years.

During the COVID-19 pandemic, an increase in the incidence of T1DM has been observed globally [10, 11, 12, 13, 14], as well as in Serbia [15, 16]. However, based on currently available data, it is inconclusive whether this is due to a direct (virus-triggered autoimmune response) or indirect (stress, lack of physical activity) impact of COVID-19 [10,13, 17, 15–21].

In General Hospital “Dr Laza K. Lazarević” in Šabac, which serves the children from the Mačva District, the average ten-year incidence of T1DM in children aged 0–19 years is at 14.80 per 100,000 for the period 2013–2022.

The highest incidence was recorded in the age group of 10–14 years, and the lowest in the age group of 15–19 years, which is consistent with previously published data on the incidence of T1DM in Serbia [4]. No statistically significant difference was observed between sexes in the incidence of T1DM in children, which is also consistent with existing literature, stating that sex is not a risk factor for the onset of T1DM in children [22].

Statistical analysis of the data did not reveal a statistically significant difference in the incidence of T1DM in the years before and during the COVID-19 pandemic, although we did notice that the incidence was higher in 2021 and 2022 compared to all previous years.

In the period after 2020, the majority of children and adolescents were antigen-negative for SARS-CoV-2 (only one child tested positive), five children had a history of contact with COVID-19 patients, and one adolescent had recovered from COVID-19. However, we do not have data on the presence of SARS-CoV-2 antibodies in our patient population; therefore, we were unable to investigate any clear linkage between T1DM incidence and the autoimmune or non-autoimmune effects of SARS-CoV-2 infection. In our patient population, 25.9% of children were in DKA at the time of diagnosis in the period prior to the COVID-19 pandemic (2013–2019), while 24.0% of children were in DKA at the time of diagnosis during the pandemic (2020–2022). Statistical analysis showed no statistically significant difference in the frequency of DKA in newly diagnosed children in the period before the COVID-19 pandemic compared to the period during the pandemic, unlike data obtained in the Vojvodina [15] and Niš [16] regions.

## ***Conclusion***

Based on the data from our research, we can conclude that the COVID-19 pandemic has, in fact, had a certain impact on the occurrence of T1DM in children.

Although we were unable to fully examine the direct impact of the Sars-Cov-2 virus, we believe that the exposure of children to stress, isolation, and reduced physical activity during the COVID-19 pandemic—which are known risk factors for T1DM—have had a greater impact than the Sars-Cov-2 virus itself as a trigger for the immune response in children.

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Conflicts of Interest: The authors declare no conflict of interest.