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UTICAJ COVID-19 PANDEMIJE NA INCIDENCIJU DIJABETESA TIP 1 KOD DECE I ADOLESCENATA U OPŠTOJ BOLNICI „DR LAZA K. LAZAREVIĆ“ ŠABAC

Sažetak: *Uvod i ciljevi:* Tokom poslednjih godina uočen je porast incidencije dijabetes melitus tipa 1 širom sveta, naročito tokom pandemije COVID-19. Cilj našeg istraživanja je da prikazemo incidenciju dijabetes melitus tipa 1 u Opštoj bolnici „Dr Laza K. Lazarević“ u Šapcu i uticaj pandemije COVID-19. *Metodologija:* U Opštoj bolnici „Dr Laza K. Lazarević“ u Šapcu gravitira 35.141 dete uzrasta 0–19 godina sa teritorije Mačvanskog okruga. Podaci su skupljeni retrospektivnom analizom elektronskih medicinskih kartona dece i adolescenata kod kojih je postavljena dijagnoza dijabetes melitus tipa 1 u Opštoj bolnici „Dr Laza K. Lazarević“ u Šapcu od januara 2013. do decembra 2022. godine. *Rezultati:* Tokom ovog desetogodišnjeg perioda prosečna incidencija dijabetes melitus tipa 1 kod dece <19 godina bila je 14,80/100,000, sa najvišom incidencijom u uzrasnoj grupi od 10 do 14 godina, a najmanjom u uzrasnoj grupi od 15 do 19 godina. U godinama tokom pandemije COVID-19 zabeležena je nešto viša incidencija u odnosu na godine pre pandemije, ali bez statistički značajne razlike. *Zaključak:* Na osnovu podataka dobijenih našim istraživanjem možemo uočiti da je COVID-19 pandemija imala izvesnog uticaja na pojavu dijabetes melitus tipa 1 kod dece, jer je udružena sa višom incidencijom u odnosu na godine pre pandemije COVID-19.

Cljučne reči: tip 1 dijabetes melitus, deca, incidencija, COVID-19

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 T1DM

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in children and adolescents at General Hospital “Dr Laza K. Lazarevic” in Sabac, as well as the impact of the COVID-19 pandemic. *Methodology:* General Hospital “Dr Laza K. Lazarevic” in Sabac 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 Type 1 Diabetes Mellitus at the hospital 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’s clear that the COVID-19 pandemic has had some impact on the emergence of Type 1 Diabetes Mellitus in children, as it is associated with a higher incidence of Type 1 Diabetes Mellitus compared to the years preceding the COVID-19 pandemic.

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

Uvod

Dijabetes melitus tip 1 (T1DM) je rezultat interakcije genetskih, ekoloških i imunoloških faktora, koji na kraju dovode do uništenja beta ćelija pankreasa i posledičnom nedostatku insulina. Predstavlja najčešći tip dijabetesa koji se javlja kod dece i adolescenata. Usled infekcije ili delovanja stimulusa iz spoljašnje sredine započinje autoimunski proces i masa beta ćelija počinje da se smanjuje, a insulinska sekrecija biva poremećena. Smatra se da se kod ovih obolelih osoba nedostatak insulina razvija kroz mesece i/ili godine i one mogu biti podložnije razvoju ketoze [1]. U svetu se incidencija T1DM povećava brzinom 3–4% godišnje iz nejasnih razloga, a naročito tokom pandemije COVID-19 [2].

Cilj našeg istraživanja je da prikazemo incidenciju T1DM u Opštoj bolnici „Dr Laza K. Lazarević” u Šapcu i uticaj pandemije COVID-19.

Metodologija

Podaci su skupljeni retrospektivnom analizom elektronskih medicinskih kartona dece i adolescenata kod kojih je postavljena dijagnoza T1DM u Opštoj bolnici „Dr Laza K. Lazarević” u Šapcu od januara 2013. do decembra 2022.

godine. Dijagnoza je postavljena na osnovu preporuka vodiča Internacionalnog udruženja za pedijatrijski i adolescentni dijabetes (ISPAD) [3]. Sva deca i adolescenti su upućivani u nadležnu ustanovu tercijarnog nivoa, Institut za zdravstvenu zaštitu majke i deteta „Dr Vukan Čupić” u Beogradu (IMD) ili u Univerzitetsku dečiju kliniku u Beogradu (UDK), gde je dijagnoza potvrđena. Od podataka koji su analizirani su pol, uzrast u vreme postavljanja dijagnoze, datum postavljanja dijagnoze, prisustvo dijabetesne ketoacidoze (DKA); kod pacijenata kod kojih je dijagnoza postavljena nakon 2020. godine postojanje akutne infekcije virusom COVID-19 na osnovu rezultata brzog Ag testa na SARS-CoV-2, anamnestički podatak o prethodno preležanoj infekciji ili kontaktu sa obolelima od COVID-19. Postojanje DKA u momentu postavljanja dijagnoze je utvrđeno na osnovu postojanja nivoa glukoze u krvi >11 mmol/L (200mg/dL), uz venski pH $<7,3$ ili nivoom bikarbonata <15 mmol/L, prisustva ketonemije ili ketonurije. Pacijenti su podeljeni u pet uzrasnih grupa: 0-4 godine, 5-9 godina, 10-14 godina i 15-19 godina. Opštoj bolnici „Dr Laza K. Lazarević” u Šapcu gravitiraju deca Mačvanskog okruga sa Opština Šabac, Koceljeva, Vladimirci i Bogatić. Prema nacionalnom popisu stanovništva iz 2011. godine, na ovoj teritoriji bilo je 35.141 dete uzrasta 0-19 godina; na teritoriji Opštine Šabac 23.360; teritoriji Opštine Koceljeve 2.567; teritoriji Opštine Vladimirci 3.298; teritoriji Opštine Bogatić 5.916. Ovi podaci su korišćeni za izračunavanje incidencije T1DM u periodu od januara 2013. do decembra 2022. godine.

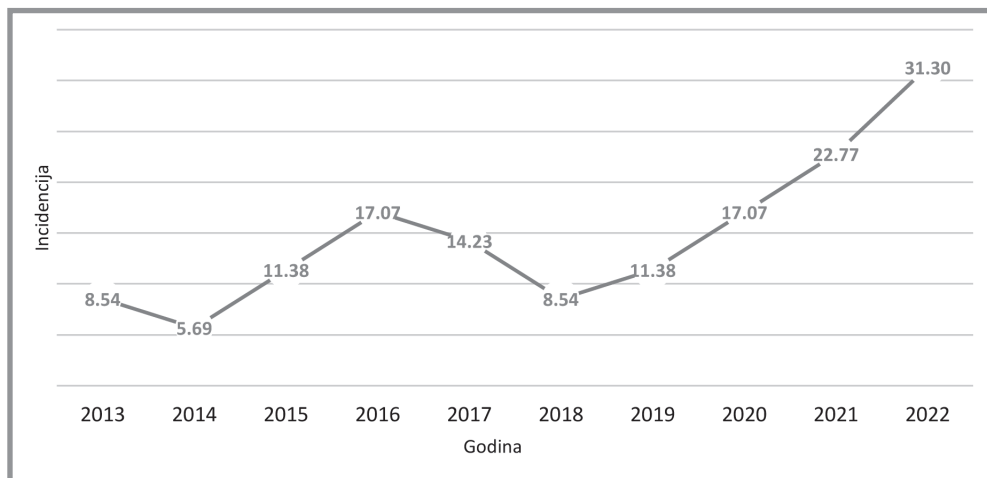
Statistika

U statističkoj analizi korišćene su deskriptivne i analitičke statističke metode. Sve statističke analize rađene su korišćenjem SPSS softverskog paketa, verzija 23. Značajnost je definisana za nivo $p < 0,05$. Rezultati su prikazani tabelarno i grafički.

Etički odbor Opšte bolnice „Dr Laza K. Lazarević“ Šabac dao je saglasnost za realizaciju istraživanja.

Rezultati

Tokom ovog desetogodišnjeg perioda identifikovano je 52 pacijenta uzrasta 0-19 godina sa novootkrivenim T1DM, sa prosečnom desetogodišnjom incidencijom od 14,80 na 100,000 (grafikon 1, tabela 1).



Grafikon 1. Incidencija T1DM u Mačvanskom okrugu, u periodu 2013-2022.

Tabela 1. Incidencija T1DM po opštinama Mačvanskog okruga

		2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Ukupno
Opština Šabac	broj	3	1	2	5	2	3	3	4	6	9	38
	incidencija	12,84	4,28	8,56	21,40	8,56	12,84	12,84	17,12	25,68	38,53	162,67
Opština Koceljeva	broj	0	0	1	0	2	0	0	1	1	1	6
	incidencija	0	0	38,96	0	77,91	0	0	38,96	38,96	38,96	233,74
Opština Vladimirci	broj	0	1	1	1	0	0	0	1	0	1	5
	incidencija	0	30,32	30,32	30,32	0	0	0	30,32	0	30,32	151,61
Opština Bogatić	broj	0	0	0	0	1	0	1	0	1	0	3
	incidencija	0	0	0	0	16,90	0	16,90	0	16,90	0	50,71
Mačvanski okrug	broj	3	2	4	6	5	3	4	6	8	11	52
	incidencija	8,54	5,69	11,38	17,07	14,23	8,54	11,38	17,07	22,7	31,30	147,98 (14,80*)

*-prosečna desetogodšnja incidencija T1DM na 100.000

Muškog pola bilo je 29/52 pacijenta (55,8%), ženskog pola bilo je 23/52 pacijenta (44,2%) (tabela 2). Statističkom analizom podataka nije uočena statistički značajna razlika u pojavi T1DM u odnosu na pol (χ^2 test; $p = 0,539$).

Tabela 2. Incidencija T1DM kod dece različitog pola

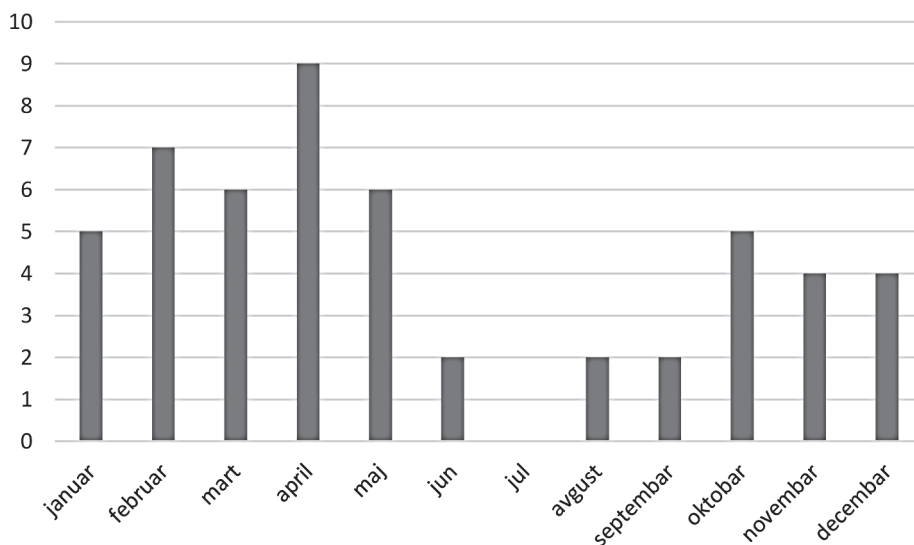
pol	muški	ženski	ukupno	p
broj	29	23	52	0,539
%	55,8%	44,2	100	
populacija	18332	16809	35141	
srednja incidencija	15,82	13,86	14,80	

Najviša incidencija zabeležena je u uzrasnoj grupi 10–14 godina, a najmanja u uzrasnoj grupi 15–19 godina (tabela 3).

Tabela 3. Incidencija T1DM po uzrasnim grupama u Mačvanskom okrugu u periodu 2013–2022.

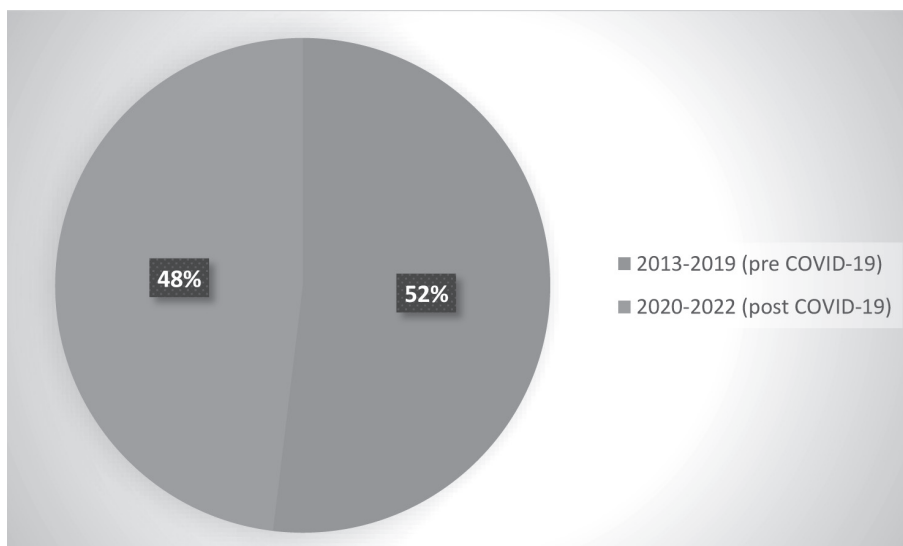
Uzrasna grupa	0–4 godina	5–9 godina	10–14 godina	15–19 godina
broj	9	16	20	7
%	17,3	30,8	38,5	13,5
populacija	7714	8858	8620	9949
srednja incidencija	11,67	18,06	23,20	7,03

Broj novootkrivenih slučajeva za svaki mesec u godini pokazao je sezonsku distribuciju sa najmanjom incidencijom od juna do oktobra (grafikon 2).



Grafikon 2. Sezonska distribucija T1DM dece uzrasta 0–19 godina

U periodu 2020–2022. tokom pandemije COVID-19 broj novootkrivenih slučajeva je 25/52 (48,1%), od kojih je 1/25 (25,0%) pacijent preležao COVID-19 infekciju, 1/25 (25,0%) je imao akutnu infekciju, 5/25 (20,0%) je bilo u kontaktu sa obolelim od COVID-19. Statističkom analizom podataka nismo uočili statistički značajnu razliku u incidenciji T1DM u periodu pre pandemije COVID-19 (2013–2019) u odnosu na period tokom pandemije COVID-19 (2020–2022) (χ^2 test: $p = 0,782$) (grafikon 3).



Grafikon 3. Incidencija T1DM pre i tokom pandemije COVID-19

U trenutku postavljanja dijagnoze 13/52 (25%) pacijenata sa novootkrivenim T1DM je bilo u DKA; 39/52 (75%) pacijenata je bilo u kompenzovanom stanju. U periodu pre pandemije COVID-19 7/27 (25,9%) dece je bilo u DKA u momentu postavljanja dijagnoze; u periodu tokom pandemije COVID-19 6/25 (24%) dece je bilo u DKA u momentu postavljanja dijagnoze. Nije primećena statistički značajna razlika kod dece koja su se prezentovala DKA u trenutku postavljanja dijagnoze poređenjem perioda pre pandemije COVID-19 (2013–2019) i tokom pandemije COVID-19 (2020–2022) (Pearson χ^2 test; $p = 0,873$).

Diskusija

Dijabetes melitus (DM) je hronični poremećaj metabolizma, koji karakteriše hiperglikemija, uzrokovana nedostatkom ili poremećajem delovanja insulina i može se podeliti u četiri opšte kategorije: 1. tip 1 dijabetes, 2. tip 2 dijabetes, 3. specifični tipovi dijabetesa i 4. gestacijski dijabetes [1].

Tip 1 dijabetes melitus (T1DM) se obično javlja u periodu detinjstva i adolescencije, ali se može javiti bilo kada tokom života, i nastaje, najčešće, kao posledica autoimunske destrukcije β ćelija pankreasa pokrenute delovanjem faktora spoljašnje sredine, kod genetski predisponiranih osoba. Bolest prolazi kroz četiri faze, koje su posledica hronične autoimunske destrukcije β ćelija pankreasa koja uzrokuje prvo parcijalni, a potom i potpuni nedostatak insulina, a simptomi će se javiti kada je uništeno skoro 90% β ćelija pankreasa. Deca se obično prezentuju klasičnim simptomima T1DM u vidu poliurije, polidipsije, polifagije, gubitka u telesnoj masi, mada prva manifestacija bolesti mogu biti i simptomi i znaci dijabetesne ketoacidoze u vidu teške dehidracije i produbljenog disanja, koje predstavlja po život ugrožavajuće stanje ukoliko se na vreme ne prepozna i ne počne sa lečenjem [1, 3].

Osim genetskih faktora, faktori spoljašnje sredine (infektivni, nutritivni, hemijski i dr.) takođe imaju značajnu ulogu u patogenezi T1DM, odnosno u razvoju autoimunosti [3]. S obzirom na to da se infekcija virusima (prvenstveno enterovirusima) smatra jednim od najznačajnijih potencijalnih pokretača bolesti kod genetski predisponiranih osoba [2], a da je tokom pandemije COVID-19 uočen porast broja dece sa novootkrivenim T1DM, neki autori smatraju da bi i SARS-CoV-2 na sličan način mogao imati potencijala za pokretanje bolesti [4, 5, 6].

Incidencija T1DM je u porastu širom sveta globalno, a značajno varira u zavisnosti od geografskog regiona, ekonomskog standarda države i uzrasta. Uočen je značajan porast incidencije T1DM u regionima kao što su Australija, Severna Amerika i Evropa, a incidencija je značajno viša u zemljama sa visokim ekonomskim standardom (7,89/100,000), kao i kod dece uzrasta 10–14 godina (18,02/100,000) [2].

Srbija spada u grupu zemalja sa visokom incidencijom (11,82/100,000) [7] i prevalencijom (135,25/100,000) [8] T1DM kod dece i adolescenata, gde je takođe uočen porast incidencije T1DM kod dece i adolescenata [7, 9] tokom poslednjih godina.

Tokom pandemije COVID-19 širom sveta [10, 11, 12, 13, 14], kao i u Srbiji [15, 16], uočava se porast incidencije T1DM. Međutim, na osnovu trenutno dostupnih podataka ne može se pouzdano tvrditi da li se radi o direktnom (virusom pokrenut autoimunski odgovor) ili indirektnom (stres, manjak fizičke aktivnosti) uticaju COVID-19 [10, 13, 17, 15–21].

U Opštoj bolnici „Dr Laza K. Lazarević” u Šapcu, kojoj gravitiraju deca sa teritorije Mačvanskog okruga, prosečna desetogodišnja incidencija T1DM kod dece uzrasta 0–19 godina u periodu 2013–2022. je 14,80 na 100.000.

Najviša incidencija zabeležena je u uzrasnoj grupi 10–14 godina, a najmanja u uzrasnoj grupi 15–19 godina, što je u skladu sa prethodno objavljenim podacima o incidenciji T1DM na teritoriji Srbije [4].

Nismo uočili statistički značajnu razliku u pojavi T1DM kod dece različitog pola, što je takođe u skladu sa podacima iz literature, da pol nije jedan od faktora rizika za nastanak T1DM kod dece [22].

Statističkom analizom podataka nije uočena statistički značajna razlika u incidenciji T1DM u godinama pre pandemije COVID-19 i tokom pandemije COVID-19, mada smo uočili da je tokom 2021. i 2022. godine incidencija bila viša u odnosu na sve prethodne godine.

Najveći broj dece i adolescenata u periodu nakon 2020. godine bio je antigenski negativan na SARS-CoV-2 (jedno dete je bilo pozitivno), petoro dece je dalo anamnestički podatak o kontaktu sa obolelim od COVID-19, jedan adolescent je preležao COVID-19. Međutim, mi nemamo podataka o prisustvu SARS-CoV-2 antitela kod dece u našoj populaciji te nismo bili u mogućnosti da istražimo jasnu povezanost incidencije T1DM sa autoimunskim i ne-autoimunskim uticajem SARS-CoV-2 infekcije.

U našoj populaciji pacijenata u periodu pre pandemije COVID-19 (2013–2019) u DKA u momentu postavljanja dijagnoze je bilo 25,9% dece, u periodu tokom pandemije COVID-19 (2020–2022) u DKA u momentu postavljanja dijagnoze bilo je 24,0% dece, statističkom analizom nismo uočili statistički značajnu razliku u učestalosti DKA kod novodijagnostikovane dece u periodu pre pandemije COVID-19 u odnosu na period tokom pandemije COVID-19 za razliku od podataka koji su dobijeni na teritoriji Vojvodine [15] i Niša [16].

Zaključak

Na osnovu podataka dobijenih našim istraživanjem možemo uočiti da je COVID-19 pandemija imala izvesnog uticaja na pojavu T1DM kod dece. Iako mi nismo bili u mogućnosti da u potpunosti ispitamo direktan uticaj virusa Sars-Cov-2, mišljenja smo da je tokom pandemije COVID-19 izloženost dece stresu, izolacija i smanjena fizička aktivnost, koji su poznati faktori rizika za nastanak T1DM, imali veći uticaj nego sam Sars-Cov-2 virus kao pokretač imunskog odgovora kod dece.

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Konflikt interesa: Bez konflikta interesa

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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).

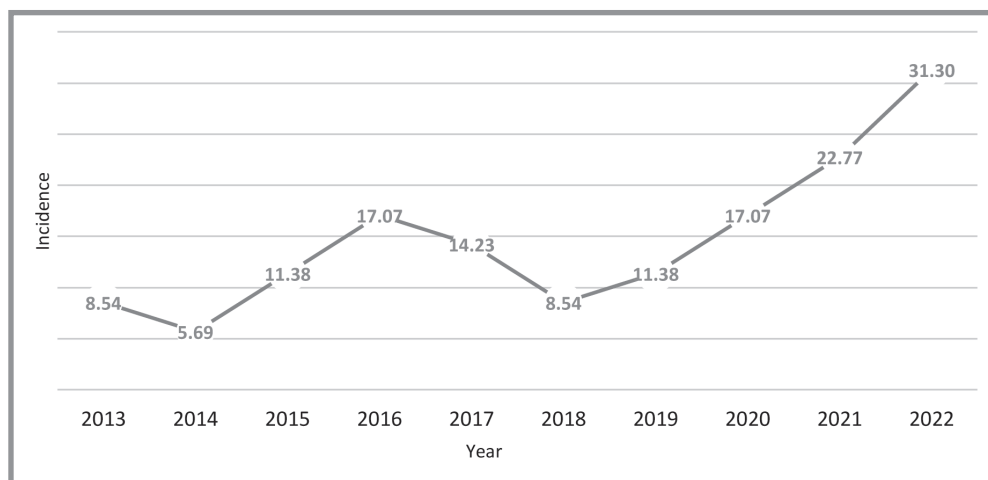


Figure 1. T1DM Incidence in the Mačva District, in the period 2013–2022

Table 1. 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 (χ^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).

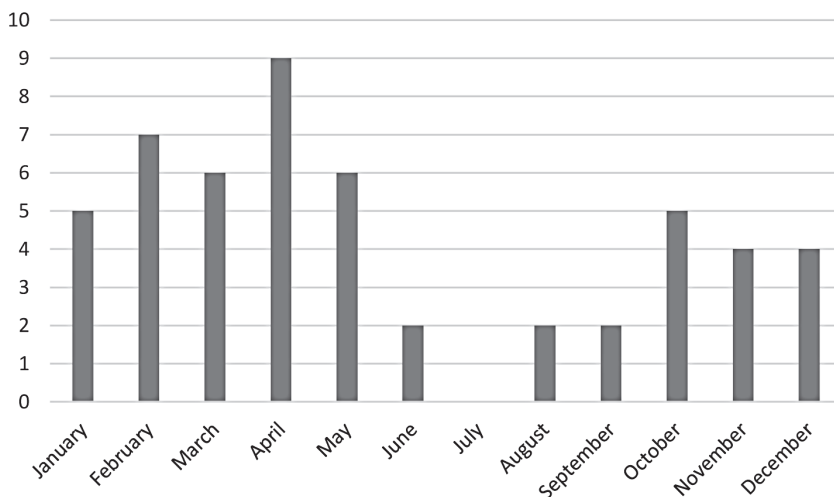


Figure 2. Seasonal distribution of T1DM in children aged 0–19 years

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).

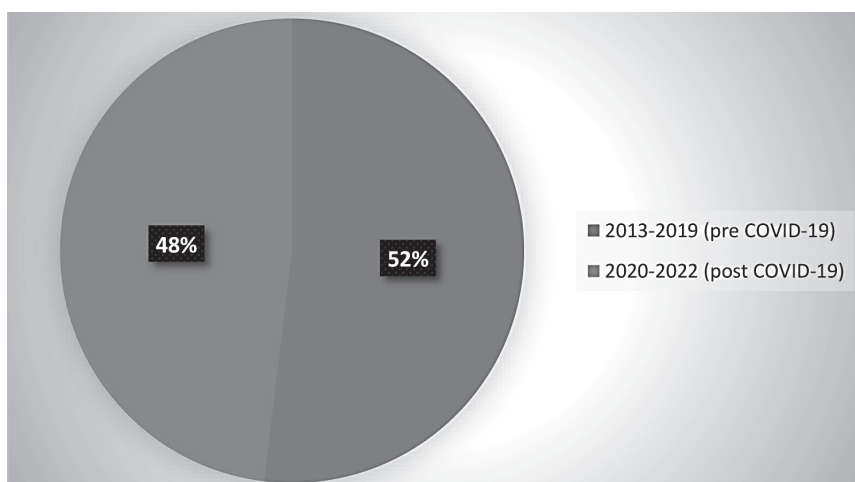


Figure 3. T1DM incidence before and during the COVID-19 pandemic

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 χ^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 β -cells triggered by environmental factors in genetically predisposed individuals. The disease progresses through four stages, driven by chronic autoimmune destruction of the β -cells in the pancreas, leading first to partial and then complete insulin deficiency. Symptoms manifest when almost 90% of the pancreatic β -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.