

THE IMPACT OF COVID-19 PANDEMIC ON TYPE 1 DIABETES MELLITUS INCIDENCE AND ITS CLINICAL PRESENTATION IN CHILDREN AND ADOLESCENTS: ONE CENTER'S EXPERIENCE

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The outbreak of the COVID-19 pandemic has a drastic impact on health systems worldwide. The aim of this research was to present the incidence and clinical picture of newly diagnosed diabetes in children in our institution during the first year COVID-19 pandemic and to compare obtained data with previous years' data. A total of 41 children were newly diagnosed with T1DM. There were two non-significant join point periods with an annual percentage increase (2007-2012: APC 8.94%), followed by a decrease (2012-2015: APC -6.88%) and a statistically significant increase (2015-2020: APC 14.20%). During the first COVID year, there was a larger number of newly diagnosed children, but without statistical significance. The percentage of children presenting with DKA in the time of T1DM diagnosis was significantly higher compared to pre COVID-19 period (84.8% vs. 34.6%; $p < 0.001$). Our results suggest a potential diabetogenic effect of the COVID-19 infection. Larger trials with long term follow ups are needed. Drastic increase in DKA at the onset of T1DM during the first COVID year urge need for better prevention measures.

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Key words: COVID-19, child, DKA

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Introduction

The outbreak of the Covid-19 pandemic has a drastic impact on health systems around the world. The introduced measures of isolation and social distancing aim to reduce the infection rate and huge influx of patients with Covid-19, hinder the normal functioning of the health care systems and increase the risk of inadequate treatment of patients with "non Covid" health problems (1).

Since the outbreak of the Covid-19 pandemic, there has been an increased influx of patients with newly diagnosed diabetes type 1 (T1DM) in a state

of severe acute complication of diabetes, diabetic ketoacidosis (DKA), observed in the everyday practice at the Pediatric Clinic in Niš. Diabetic ketoacidosis is a potentially severe, life-threatening complication of diabetes (2, 3).

The papers published thus far on this topic have provided different results regarding the incidence of type 1 diabetes in children and adolescents during the Covid-19 pandemic (4, 5). However, an increased incidence of diabetic ketoacidosis as a severe acute complication of diabetes has been reported by all cited authors (4-6).

The aim

The aim of this research was to present the incidence and clinical picture of newly diagnosed diabetes in children and adolescents in our institution during the Covid-19 pandemic between April 1st, 2020 and April 1st, 2021 and to compare the obtained data with the data of the period between 2007 and 2020.

Materials and methods

In our research, we collected and analyzed the data off patients younger than 19 years with newly diagnosed T1DM. All newly diagnosed children

with T1DM from the Southeast Serbia were referred to the Pediatric Clinic in Niš. The diagnosis of T1DM and DKA was made according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines. Data regarding subject's gender, date of birth, date of diagnosis, duration of symptoms, DKA at clinical presentation (yes/no), venous pH, glucose, and glycated hemoglobin (HbA1c) levels at diagnosis were collected retrospectively from the medical records. The methodology of our data collection was explained in detail, in an already published paper (7). Informed consents were obtained from the parents or guardians of all participants for admission to hospitals and the procedures performed during hospitalization. The study was approved by the Hospital Ethics Committee and data were retrospectively collected in accordance with the 1964 Declaration of Helsinki.

Statistical analysis

Results are expressed as percentages or means ± standard deviation (SD). The differences in the means of variables between groups were tested using the independent T test in case of normally distributed continuous variables and for non-normally distributed continuous variables, Mann-Whitney U

test. The chi squared test was used to compare occurrence of DKA and DKA severity by age categories. A statistical analysis was performed in EPI INFO v7.2.2.6 (CDC, Atlanta, USA). The trend of new T1DM cases was estimated by the join point regression analysis. Join point analyses were performed using an available software: "Join point Regression Program", Version 4.8.0.1 (Surveillance Research program, National cancer Institute, USA) (8). A p-value of $p < 0.05$ was selected as statistically significant.

Results

There were 349 children newly diagnosed with T1DM1 in the period from 2007 to 2020 (Table 1). During this period there were two non-significant join point periods with an annual percentage increase (2007-2012: APC 8.94%), followed by a decrease (2012-2015: APC -6.88%) and a statistically significant increase (2015-2020: APC 14.20%) (Figure 1).

During the first Covid-19 year there were a larger number of newly diagnosed children, but without statistical significance. Most newly diagnosed cases were during the fall and winter months (Figure 2).

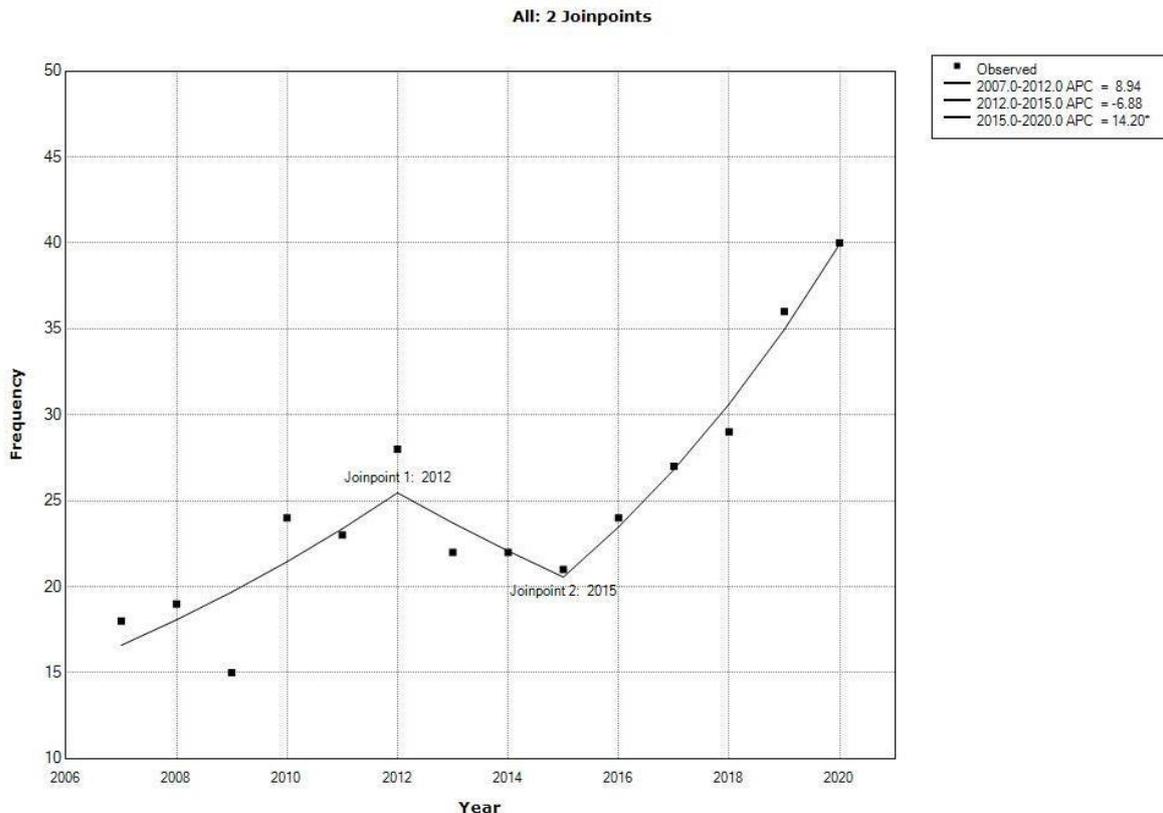


Figure 1. Join-point regression analysis of new cases in the period 2007-2020

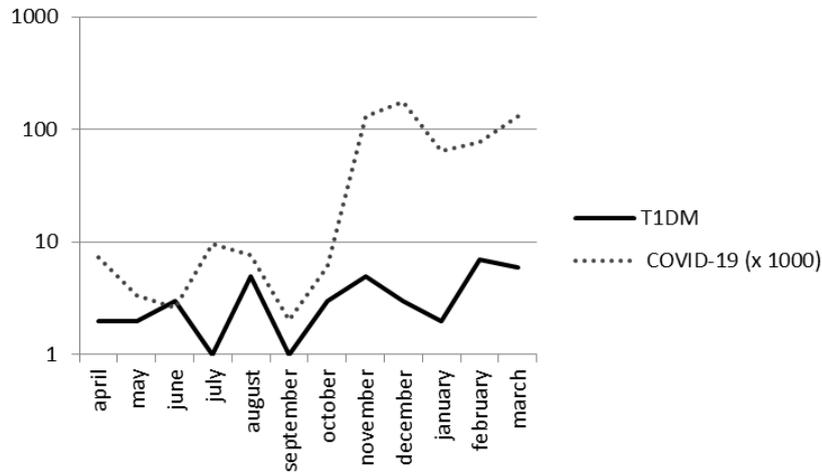


Figure 2. Number of T1DM and COVID-19 patients 2020/21

Table 1. Total number of newly T1DM diagnosed patients

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Covid 19	TOTAL
Count	18	19	15	24	23	28	22	22	21	24	27	29	36	41	349
%	5.0	5.3	4.2	6.7	6.4	7.8	6.1	6.1	5.9	6.7	7.5	8.1	10.3	11.7	100.0

Table 2. Demographic and clinical characteristics

	Before 2020		Covid year		p ¹
Gender					
Boys	173	54.6	23	56.1	0.986
Girls	144	45.4	18	43.9	
Age					
Mean ± SD	9.61 ± 4.21		9.20 ± 4.64		0.785 ²
Median (IQ)	9.63 (6.72)		10.39 (8.66)		
Min-Max	0,34-18,40		0.52-15.79		
Age groups					
< 6	71	23.6	12	29,3	0.254
6-11	112	37.2	10	24.4	
> 12	118	39.2	19	46.3	
Clinical status					
Compensate state	187	63.4	5	15.2	< 0.01
DKA	99	34.6	30	84.8	
DKA severity					
Mild DKA	128	44.8	9	27.3	
Moderate DKA	25	8.7	7	21.2	
Severe DKA	34	11.9	12	36.4	< 0.001
Blood glucose	22.04 ± 8.93		24.28 ± 8.92		0.135 ²
Hba1c	12.25 ± 8.02		12.06 ± 2.12		0.252 ²
Duration of symptoms	19.37 ± 18.87		19.32 ± 15.01		0.732 ²

¹ Chi-square test, ² Mann-Whitney test

The baseline demographics and clinical characteristics at the time of diagnosis are presented in Table 1. The mean age at presentation, gender distribution, and duration of self-reported symptoms were similar between the two periods. Blood glucose and HbA1c levels were comparable.

During the Covid-19 pandemic, the number of children presenting with DKA in the time of T1DM diagnosis was significantly higher compared to the pre Covid-19 period (84.8% vs. 34.6%; $p < 0.001$), representing an absolute increase of 50.5% (Table 1).

The prevalence of severe DKA at DM1 onset was also significantly higher during the pandemic period, compared to the control (36.4% vs. 11.9%; $p < 0.001$), representing an absolute increase of 24.5% (Table 2).

Discussion

In the Republic of Serbia, there is a significant increase in the incidence of diabetes in children and adolescents aged 0 to 19 in the period between 2007 (8.09/100,000) and 2016 (16.31/100,000) (7, 9, 10). In our research, there is a significant increase of newly diagnosed patients between 2015 and 2020 year. This increase is also evident during the first Covid-19 year, but with no statistical difference. Such a rapid increase in the incidence cannot be attributed to changes in the genetic structure of the population. The main reasons for the increase in the incidence can be attributed to the change in exposure to environmental factors (11, 12). There are numerous risk factors for the development of T1DM, and viral infections certainly play one of the major roles in its pathogenesis. Since the COVID-19 pandemic was announced by the World Health Organization on March 11th, 2020, a large number of patients have been diagnosed with this infection in our region. On the other hand, due to the closure of collective spaces, there are fewer cases of other virus infections. Stress exposure is increased, children are isolated and physical activity is reduced, which are additional risk factors (13-15). During the Covid-19 pandemic, most newly diagnosed cases were during the fall and winter months (14). Figure 2 displays the parallel number of Covid-19 patients

and newly diagnosed T1DM children. Our results suggest a potential diabetogenic effect of the COVID-19 infection. The expression of ACE2 on pancreatic β cells may potentially lead to β cell damage by the virus and result in insulin deficiency (16, 17). The sparse literature data however cannot exclude the delay between immunologic factors activation due to Covid-19 infections and the onset of T1DM (18).

Recent papers investigating the incidence of T1DM during the Covid-19 pandemic have given different results. German study demonstrated an increasing incidence of T1DM in this country since 2011 (5). However, this study failed to demonstrate any pandemic related short-term changes in T1DM. Unsworth et al. found an increase in new T1DM cases between March, 2020 and June, 2020 comparing with T1DM cases in the previous five years (4).

Previously published studies have shown the prevalence of DKA in about 35% of newly diagnosed patients with T1DM in our hospital (10, 19). A delay in diagnosis of children with new onset DM1 during the COVID-19 pandemic could be due to possible fears regarding the viral transmission during health-care appointments. Additionally, the under-recognition of secondary symptoms could be due to reduced face-to-face interactions with medical providers. Clinicians may have been more prone to assess infectious and respiratory symptoms for a possible Covid-19 diagnosis, rather than considering the new onset of DM1. With laboratory resources being targeted towards Covid-19 diagnosis, clinicians may have been reluctant to pursue lab testing for blood glucose or urinalysis.

Conclusion

Our results suggest a potential diabetogenic effect of the Covid-19 infection. The sparse literature data however cannot exclude the delay between immunologic factors activation due to Covid-19 infections and the onset of T1DM. Larger trials with long term follow ups are needed. Drastic increase in DKA at the onset of T1DM during Covid-19 year urge the need for better prevention trough patients and medical staff re-education.

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UTICAJ PANDEMIJE VIRUSA COVID-19 NA UČESTALOST I KLINIČKU PREZENTACIJU DIJABETESA TIP 1 KOD DECE I ADOLESCENATA: ISKUSTVO JEDNOG CENTRA

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Pandemija virusa COVID-19 drastično je promenila funkcionisanje zdravstvenog sistema. Cilj našeg istraživanja je da prikaže incidenciju i kliničku prezentaciju dece i adolescenata sa novootkrivenim tipom 1 šećerne bolesti (DM tip 1) tokom prve godine pandemije virusa COVID-19 i da dobijene podatke uporedi sa podacima iz prethodnih godina. Tokom ispitivanog perioda, dijagnostikovano je 41 bolesnik. Joint point analizom utvrđen je godišnji porast u periodu od 2007. do 2012. godine (APC 8,94%), praćen smanjenjem broja u periodu od 2012. do 2015. godine (APC 6,88%) i statistički značajnim uvećanjem od 2015. do 2020. godine (APC 14,20%). Broj novoobolele dece tokom prve godine COVID-19 pandemije bio je veći, ali bez statističke značajnosti. Procenat dece sa dijabetesnom ketoacidozom (DKA) u vreme postavljanja dijagnoze DM tip 1, u ispitivanom periodu, bio je značajno veći nego u prethodnim godinama (84,8% prema 34,6%; $p < 0,001$). Naši rezultati ukazuju na potencijalno dijabetogeni efekat COVID-19 virusa. Potrebne su opsežnije i dugotrajnije studije da bi se utvrdile prave dimenzije ovog uticaja. Drastičan porast DKA u vreme postavljanja dijagnoze DM tip 1, tokom pandemije COVID-19 virusa zahteva poboljšanje preventivnih mera.

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Ključne reči: COVID-19, deca, DKA