Na osnovu člana 9 i stava 3 člana 31 a Pravila doktorskih studija (Bilten Univerziteta Crne Gore broj:513/20 i 561/22), a nakon razmatranja Drugog godišnjeg izvještaja mentora prof. dr Mire Samardžić o napredovanju doktoranda dr med Maje Raičević broj:1955 od 24.11.2022.godine, Komisija za doktorske studije na sjednici održanoj dana 14.12.2022. godine je donijela

O D L U K U

1. Predlaže se Vijeću Medicinskog fakulteta da usvoji Drugi godišnji izvještaj mentora prof. dr Mire Samardžić o napredovanju doktoranda dr med Maje Raičević broj: 1955 od 24.11.2022. godine.

2. Prijedlog komisije i Izvještaj mentora sa objavljenim radovima iz tačke jedan ove Odluke, dostavljaju se Vijeću Medicinskog fakulteta, na dalje izjašnjenje.

Obrazloženje

U skladu sa stavom 1 člana 31a Pravila doktorskih studija, mentor prof. dr Mira Samardžić, blagovremeno je dostavila izvještaj o napredovanju doktoranda dr med Maje Raičević, broj 1955 od 24.11.2022. godine.

Na osnovu stava 3 člana 31 a Pravila doktorskih studija, Komisija za doktorske studije na sjednici održanoj dana 14.12.2022. godine, nakon razmatranja navedenog izvještaja mentora, konstatovala da izvještaj sadrži sve elemente, da je pravilno popunjen i na osnovu njega se stiče konkretan uvid o ostvarenom napretku kandidatkinje. Mentor je visokim ocjenama okarakterisao dosadašnji istraživački rad doktorantkinje i dostavio objavljene radove kao rezultat doktorskih istraživanja. Priloženi podaci u IM obrascu ukazuju na posvećenost kandidatkinje.

Na osnovu navedenog Komisija je odlučila kao u dispozitivu ove Odluke.

DOSTAVLJENO
-Vijeću Medicinskog fakulteta
-Studentskoj službi

KOMISIJA ZA DOKTORSKE STUDIJE
PREDSJEDNIK

Prof. dr Filip Vukmirović

GODIŠNJI IZVJEŠTAJ MENTORA O NAPREDOVANJU DOKTORANDA

Akademska godina za koju se podnosi izvještaj	2022/2023		
OPŠTI PODACI O DOKTORANDU			
Titula, ime, ime roditelja, prezime	dr med. Maja (Ranko) Raičević		
Fakultet	Medicinski fakultet		
Studijski program	Medicina		
Broj indeksa	9/14		
MENTOR/MENTORI			
Prvi mentor	Prof. dr Mira Samardžić	Medicinski fakultet, Univerzitet Crne Gore, Crna Gora	Pedijatrijska endokrinologija
Drugi mentor	/	/	/

EVALUACIJA DOKTORANDA*					
Koliko ste zadovoljni kvalitetom održanih susreta sa doktorandom?	☐ 1	☐ 2	☐ 3	☐ 4	☒ 5
(Ako je prethodni odgovor „1“ ili „2“ dati obrazloženje i prijedloge za poboljšanje)					
Da li je definisan plan rada sa doktorandom?	☒ DA	☐ NE			
Da li je doktorand ostvario napredak prema predviđenom planu rada?	☒ DA	☐ NE			
(Ako je prethodni odgovor „ne“ dati obrazloženje i prijedloge za poboljšanje)					
Kvalitet napretka doktorandovog istraživačkog rada u periodu između dva izvještaja je:	☐ 1	☐ 2	☐ 3	☐ 4	☒ 5
(Ako je prethodni odgovor „1“ ili „2“ dati obrazloženje i prijedloge za poboljšanje)					
Dati ocjenu doktorandove spremnosti za konsultacije.	☐ 1	☐ 2	☐ 3	☐ 4	☒ 5
Dati ocjenu planiranja i izvršavanja godišnjih istraživačkih aktivnosti i stručnog usavršavanja doktoranda.	☐ 1	☐ 2	☐ 3	☐ 4	☒ 5
Dati ocjenu napretka u savladavanju metodologije naučno-istraživačkog rada.	☐ 1	☐ 2	☐ 3	☐ 4	☒ 5
Dati ocjenu o aktivnostima sprovedenim na pisanju i objavljivanju naučnih radova.	☐ 1	☐ 2	☐ 3	☐ 4	☒ 5
Dati ocjenu doktorandovog generalnog odnosa prema studijama.	☐ 1	☐ 2	☐ 3	☐ 4	☒ 5
Dati ocjenu ukupnog kvaliteta doktorandovog rada.	☐ 1	☐ 2	☐ 3	☐ 4	☒ 5

* Ocjene su: 1 – nedovoljan, 2 – dovoljan, 3 – dobar, 4 – vrlo dobar, 5 – odličan

(Ako je prethodni odgovor „1" ili „2" dati obrazloženje i prijedloge za poboljšanje)	
SAGLASNOST ZA NASTAVAK STUDIJA	
Može li doktorand nastaviti studije?	☒ Da ☐ Da, uz određene uslove ☐ Ne
(Ako je prethodno dat odgovor pod „b)" ili „c)" dati obrazloženje i prijedloge za poboljšanje)	
Napomene	
/	

IZJAVA MENTORA

Doktorantkinja je u fazi izrade pisanog dijela rada. Završetak doktorske disertacije i javna odbrana planirani su za drugu polovinu 2023. godine, što opravdano odstupa od prvobitnog gantograma aktivnosti zbog angažovanja kandidatkinje tokom COVID-19 pandemije i odlaska na užu specijalizaciju iz oblasti endokrinologije. Svakako, konsultacije sa mentorom su se redovno obavljale, pri čemu su se definisale aktivnosti koje je kandidatkinja redovno ispunjavala.

U međuvremenu, kandidatkinja je objavila dva rada iz doktorske disertacije. Prvi, pod nazivom „Trends in nationwide incidence of pediatric type 1 diabetes in Montenegro during the last 30 years", objavljen je u međunarodnom časopisu Frontiers in Endocrinology, koji pripada Q1 kategoriji časopisa i nalazi se na SCI listi, sa impakt faktorom 6,05. Drugi rad iz doktorske disertacije pod nazivom „Quality of Life of Elementary School Students with Type 1 Diabetes in a Developing Country during the COVID Pandemic" objavljen je u časopisu International Journal of Enviromental Research and Public Health", koji pripada Q1 kategoriji časopisa i nalazi se na SCI listi, sa impakt faktorom 4,614.

Shodno svemu navedenom, saglasna sam da kandidatkinja nastavi izradu svoje doktorske disertacije.

1. Raicevic M, Samardzic M, Soldatovic I, Curovic Popovic N, Vukovic R. Trends in nationwide incidence of pediatric type 1 diabetes in Montenegro during the last 30 years. Front Endocrinol (Lausanne). 2022 Sep 6;13:991533. doi: 10.3389/fendo.2022.991533.
2. Raicevic, M.; Obradovic, A.; Samardzic, M.; Raicevic, M.; Curovic Popovic, N.; Panic Zaric S. Quality of Life of Elementary School Students with Type 1 Diabetes in a Developing Country during the COVID Pandemic. Int. J. Environ. Res. Public Health 2022, 19, 14873. https://doi.org/10.3390/ijerph1922148 73.

U Podgorici,
24.11.2022.godine

prof.dr Mila Samardžić

International Journal of
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Article

Quality of Life of Elementary School Students with Type 1 Diabetes in a Developing Country during the COVID Pandemic

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Abstract: Type 1 diabetes (T1D) is a condition that affects all aspects of life, and thus is closely related to the quality of life itself. Dealing with it during the COVID-19 pandemic is a big challenge. A case–control study conducted in Montenegro at the end of 2021 included 87 elementary school students with T1D and 248 of their peers as controls matched by gender. Standardized questionnaires were distributed to participants (Peds-QL Generic core 4.0 questionnaire for all participants and Peds-QL Diabetes Module 3.2 only for cases). Based on them, the results of obtained scores were measured and compared using non-parametric statistical methods in relation to gender, region and type of household. Children with T1D reported lower quality of life comparing to matching controls with lower scores in almost all domains. Differences in the same domains among patients and their classmates were also observed in the different gender subgroups, environment type subgroups and in the central region. Results of the study provide insights to prioritizing actions for children with diabetes care as well as for public healthcare planning.

Keywords: diabetes mellitus; T1D; quality of life; HRQoL; COVID; students

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1. Introduction

After being diagnosed with type 1 diabetes (T1D) children challenge many difficulties; they have to make corrections in food intake and physical activity, repeatedly check blood glucose during the day and night, get multiple insulin injections, all to target optimal glycemic range and best possible quality of life (QoL).

QoL is acknowledged as an important indicator of diabetes care outcome, but also as an indicator of public health functioning [1,2]. It is influenced by many health-related, environmental and social factors.

Children with type 1 diabetes, in comparison to their healthy peers, are challenged more frequently with depressive and anxiety disorders, which can be insulin-induced and lead to their poor metabolic control and lower quality of life [3,4].

Many research papers suggested that since the SARS-CoV-2 virus has been spread throughout the world, the COVID-19 pandemic significantly negatively impact the health-related quality of life (HRQoL) of children and adolescents [5,6]. It could be due to school closures, social distancing, changes in family environment, sedentary lifestyle, etc [7]. It was previously reported that during COVID-19 pandemic children and adolescents were frequently coping with mental disturbances such as anxiety, depression, stress, loneliness and tension [8].

There are scarce data on the impact of the COVID-19 pandemic on QoL of children with chronic diseases, such as T1D, although awareness about the risk of their disease during COVID-19 pandemic was raised. It is observed that patients with diabetes are in higher risk of severe presentation of COVID-19, the need for mechanical ventilation and mortality [9].

The aim of this study is to evaluate the QoL of elementary school students in Montenegro with T1D and to compare it with QoL of their peers, during the COVID-19 pandemic.

2. Materials and Methods

During November and December 2021, the medical records of all patients diagnosed under the age of 15 with new-onset T1D, between January 1992 and April 2021 in Montenegro, was evaluated. 135 of them were elementary school students at the moment of study, aged 5–15. This study involved 90 of them who had regular check-ups in the endocrinology department of the Institute for Children's Diseases, Clinical Center of Montenegro (where they have appointments every 3–4 months) as cases. They were offered the QoL questionnaires. Three families disagreed to participate in the study (two because of feeling unpleasant to participate and the third one because of being unlettered). A total of 335 elementary school students participated in the study, 87 (26.0%) were cases. A control group was formed of patients` classmates, without diabetes, who were matched by gender with a case–control ratio 1:3. After parent or caregiver signed the consent for participation, questionnaires were distributed to the patients' school for the control group. To reduce bias, controls were elected as the first three of the same gender as their classmate with T1D, encountered in Teacher Diary among ordinal numbers 5 and 15. All participants completed the questionnaires independently.

Participants were divided into groups regarding their place of residence, based on the type of the surrounding (rural/urban) and geographical region. It is an important point of this research, because of the availability of healthcare resources which are lacking in rural areas, especially in the northern part of the country. Differences among regions concern economic resources and life standard, which is highest in the south region and lowest in the north region of Montenegro.

The approvals of the Ethical committee of Clinical Center of Montenegro, Ministry of Education of Montenegro and Bureau for Education of Montenegro were obtained.

The measurement tool was a standardized Peds-QL Generic core 4.0 questionnaire, covering 4 domains: physical health (8 questions), emotional health (5 questions), social functioning (5 questions) and school functioning (5 questions) [10]. Peds-QL Diabetes Module 3.2 is a diabetes-specific pediatric questionnaire authored by Varni et al. and for the purpose of this research, the Montenegrin language version was validated by MAPI Research Trust. It was filled up only by patients with T1D and it covers 5 domains: diabetes (15 questions), barriers to therapy (5 questions), adherence to therapy (6 questions), worry (2 or 3 questions/depending on age), and communication (4 questions) [11]. Each question is graded 0–4 (0-never, 1-almost never, 2-sometimes, 3-often and 4-almost always), then points are added to these values: 0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0. At the end, all points are added together, so the higher score the better the quality of life. Both, children with diabetes and control group filled out the Questionnaire for general data (age, place of residence, education, employment of the parents and their marital status). Data about metabolic control and insulin therapy were taken from the patient's medical records.

EZR (Easy R) plugin (version 1.42) on R Commander (version 2.6–2) was used for descriptive statistics of the collected data and for analytic statistical data processing, to compare patients' with control group reports, primarily for comparing medians with Mann–Whitney U test (due to data lack of normal distribution) and calculating the correlation coefficient (Spearman). The selected significance level was $p < 0.05$.

3. Results

The control group was smaller (248) than planned (87 × 3 = 261) because in some rural areas were not enough students in the same class or even grade. Median of age in years was 12.4. Among participants 61.2% were boys. In the central region of Montenegro lived 48.1%, predominantly in urban surroundings (77.3%) (Table 1).

Table 1. Summary of participants' socio-demographic characteristics.

	Cases (n = 87)	Controls (n = 248)	Total (n = 335)
Male %	62.1	60.9	61.2
Female %	37.9	39.1	38.8
Urban %	73.6	78.6	77.3
Rural %	26.4	21.4	22.7
Central Region %	48.3	48.0	48.1
North Region %	23.0	21.8	22.1
South Region %	28.7	30.2	29.9
Median of age in years (IQR)	12.41 (10.4–13.4)	12.1 (10.7–13.1)	12.2 (10.6–13.1)

Children with T1D reported lower HRQOL than their matching controls (Table 2). They had significantly lower scores in domain of emotional and school functioning, as well as lower Psychosocial Health Summary Score. Differences in the same domains among patients and their classmates were also observed in the different gender subgroups, environment type subgroups and in the central region. Controls living in the north and south region of the country did not have better emotional functioning comparing to their peers with diabetes.

Table 2. Medians (IQR) of scores by sociodemographic status and by case/control status.

		Physical Functioning	Emotional Functioning	Social Functioning	School Functioning	Psychosocial Health Summary	Physical Health Summary	Total Score
T1D Status	Case	90.6 (81.3–100)	80 (62.5–90)	100 (85–100)	75 (65–85)	81.7 (72.5–90)	90.6 (81.3–100)	85.9 (76.1–91.3)
	Control	93.7 (87.5–100)	85 (75–95)	100 (90–100)	90 (80–100)	90.8 (83.3–96.7)	93.8 (87.5–100)	91.3 (84.8–95.7)
	Test *	W = 9211 (p = 0.039)	W = 7904 (p < 0.001)	W = 9874.5 (p = 0.194)	W = 4711 (p < 0.001)	W = 5835 (p < 0.001)	W = 9307.5 (p = 0.0532)	W = 6653 (p < 0.001)
Male	Case	90.6 (81.3–100)	80 (65–90)	100 (90–100)	70 (60–85)	80.8 (73.3–90)	90.6 (81.3–100)	86.4 (76.1–91.3)
	Control	93.8 (87.5–100)	90 (80–100)	100 (90–100)	90 (85–100)	91.7 (85–96.7)	93.8 (87.5–100)	91.3 (86.4–96.7)
	Test *	W = 3642.5 (p = 0.238)	W = 2908.5 (p = 0.001)	W = 3886 (p = 0.575)	W = 1563 (p < 0.001)	W = 2015.5 (p < 0.001)	W = 3700.5 (p = 0.307)	W = 2411.5 (p < 0.001)
Female	Case	87.5 (81.3–96.9)	80 (60–90)	95 (85–100)	80 (65–85)	85 (71.7–90)	87.5 (81.3–96.9)	85.9 (75–91.3)
	Control	93.8 (87.5–100)	85 (70–95)	100 (90–100)	90 (80–100)	90 (81.7–96.7)	93.8 (87.5–100)	91.3 (82.6–95.7)
	Test *	W = 1267.5 (p = 0.071)	W = 1208 (p = 0.035)	W = 1376.5 (p = 0.183)	W = 860 (p < 0.001)	W = 973 (p < 0.001)	W = 1267.5 (p = 0.071)	W = 1034.5 (p = 0.002)
Urban	Case	87.5 (81.3–100)	80 (60–90)	100 (85–100)	77.5 (65–85)	80.8 (72.9–90)	87.5 (81.3–100)	85.3 (75.8–91.3)
	Control	93.8 (87.5–100)	85 (75–95)	100 (90–100)	90 (80–100)	90 (84.2–96.7)	93.8 (87.5–100)	91.3 (85.3–95.6)
	Test *	W = 5055 (p = 0.021)	W = 4550 (p = 0.001)	W = 5560.5 (p = 0.150)	W = 2752.5 (p < 0.001)	W = 3278.5 (p < 0.001)	W = 5135 (p = 0.031)	W = 3744 (p < 0.001)
Rural	Case	93.8 (84.4–100)	80 (70–90)	100 (92.5–100)	65 (60–82.5)	83.3 (73.3–88.3)	93.8 (84.4–100)	87 (79.3–90.8)
	Control	93.8 (87.5–100)	90 (80–100)	100 (90–100)	90 (80–100)	91.7 (83.3–96.7)	93.8 (87.5–100)	92.4 (82.6–97.8)
	Test *	W = 580.5 (p = 0.742)	W = 431.5 (p = 0.041)	W = 593.5 (p = 0.843)	W = 268.5 (p < 0.001)	W = 367 (p = 0.006)	W = 580.5 (p = 0.742)	W = 412.5 (p = 0.026)
al Regio	Case	87.5 (81.3–99.2)	77.5 (60–90)	100 (90–100)	70 (65–85)	80 (71.7–87.9)	87.5 (81.3–99.2)	82.6 (76.1–91.3)
	Control	93.8 (87.5–100)	85 (75–95)	100 (90–100)	90 (80–100)	90 (81.7–96.7)	93.8 (87.5–100)	91.3 (83.7–95.7)

	Test *	W = 2069 (p = 0.093)	W = 1758.5 (p = 0.004)	W = 2322.5 (p = 0.453)	W = 1175 (p < 0.001)	W = 1361.5 (p < 0.001)	W = 2063.5 (p = 0.089)	W = 1498 (p < 0.001)
North Region	Case	93.8 (87.3–100)	90 (68.8–90)	97.5 (85–100)	80 (63.8–86.3)	86.7 (76.7–90)	95.3 (87.5–100)	88.6 (82.3–91.8)
	Control	93.8 (87.5–96.9)	92.5 (80–100)	100 (95–100)	95 (85–100)	94.2 (86.7–96.7)	93.8 (87.5–95.9)	94 (86.4–97.6)
	Test *	W = 555.5 (p = 0.853)	W = 382 (p = 0.052)	W = 424.5 (p = 0.1)	W = 212.5 (p < 0.001)	W = 256.5 (p < 0.001)	W = 581 (p = 0.617)	W = 340 (p = 0.015)
South Region	Case	90.6 (81.3–100)	85 (60–90)	100 (85–100)	80 (65–85)	83.3 (73.3–90)	90.6 (81.3–100)	85.9 (75–91.3)
	Control	93.8 (87.5–100)	85 (75–100)	95 (90–100)	90 (85–100)	90 (85–95)	93.8 (87.5–100)	91.3 (87–95.1)
	Test *	W = 720 (p = 0.078)	W = 728 (p = 0.093)	W = 924.5 (p = 0.915)	W = 372 (p < 0.001)	W = 536 (p = 0.001)	W = 720 (p = 0.078)	W = 579 (p = 0.004)

* Mann-Whitney U test.

The lowest median score was observed in domain of school functioning, in rural area, as well among boys with T1D and in the central region (Table 2).

Regardless the diabetes status, with older age "physical functioning" score slumps (Table 3). This moderate negative correlation is found among girls. It is also present in urban surroundings, but as a weak (Table 3).

Table 3. Correlation between Physical functioning score and age by gender and household type.

	ρ *	p-Value
Total	−0.14	0.009
Male	0.04	0.576
Female	−0.37	p < 0.001
Urban	−0.13	0.031
Rural	−0.16	0.177

* Spearman's rank correlation coefficient.

According to the children with T1D reports and results of Peds-QL Diabetes Module, their median diabetes-related QoL score was 73.9 (IQR 64.4–82.0). The most important difficulties for patients concerned "worry" (median 58.3, IQR 50.0–75.0), followed by "barriers to therapy" (median 70.0, IQR 60.0–85.0). For only 33.7% has never been hard doing everything they need to care for diabetes, as they reported for the month before the research interview. Almost every third patient (33.7%) also reported, that at least once felt embarrassed about having diabetes during the same period.

Following, only 34.9% of patients reported that never felt weak, 54.7% reported that never had headaches, and majority of them reported feeling hungry, thirsty, "low" or "high" from time to time (Table 4).

Table 4. Patients' reports on frequency of different diabetes-related problems during the month before the research interview (n = 87).

	Percentage				
	Never	Almost Never	Sometimes	Often	Almost Always
I feel hungry	12.8	10.5	48.8	19.8	8.1
I feel thirsty	23.2	29.1	41.9	5.8	0
I have to go to the bathroom too often	45.3	32.6	17.4	3.5	1.2
I have tummy aches	39.6	29.1	26.7	2.3	2.3
I have headaches	54.7	26.7	14	3.4	1.2
I feel like I need to throw up	73.3	17.4	7	2.3	0
I go "low"	4.7	9.3	67.4	18.6	0
I go "high"	4.7	9.3	67.4	18.6	0
I feel tired	32.5	29.1	29.1	7	2.3
I get shaky	44.2	19.8	20.8	14	1.2

I get sweaty	52.3	23.3	22.1	0	2.3
I feel dizzy	62.8	23.3	10.4	2.3	1.2
I feel weak	34.9	29.1	25.6	8.1	2.3
I have trouble sleeping	70.9	18.6	4.7	2.3	3.5
I get cranky or grumpy	27.9	18.6	40.7	8.1	4.7

4. Discussion

The results of the present study estimated that children with T1D in Montenegro have lower QoL in comparison to their non-diabetic peers. It is not a novel finding [12–14]. A similar research was conducted in Montenegro almost a decade ago, and students with T1D had also lower score in domain of school functioning in comparison to control group, but we have furthermore registered significant differences in their emotional functioning and psychosocial health [13].

The results of our study are consistent with previous reported from the Bekele et al. They have interviewed 379 patients with T1D, 5–18 years old, few months prior than our study was conducted. Their results revealed likewise lower scores in children emotional and school functioning, but adequate social functioning [15]. The highest scores in domain of social functioning in our study could be due to returning to school after COVID-19 lockdown and online teaching, mentioning our study was conducted between two peaks of COVID-19 pandemic in Montenegro in a relatively "stable" epidemiological period and just before the highest number at the end of 2021 and at the beginning of 2022 [16].

Low emotional scores could be the consequence of coping with puberty, trying to become independent and manage their disease, and further being preoccupied with chronic complications of diabetes [12]. Low diabetes-related QoL is probably attributed to demands to maintain optimal metabolic control.

Remarkably low score in the section "worries", showed that elementary school students with T1D, although very young, are deeply concerned regarding their health. They have problem in school functioning, especially if they live in rural area. All of the above emphasizes the need for psychological support.

Actually, it is already known that children with T1D have significantly impaired school functioning in comparison to their peers, but we have identified that problem is larger in the central region of Montenegro and for children living in rural surroundings [12,14,17].

Furthermore, some actions are needed on raising awareness about diabetes among school staff and patients' peers, especially in central region of Montenegro and for those living in rural settings, so children with T1D would have positive self-concept. It could be diabetes training organized through workshops for staff and patients' peers with an aim to fortify their relationship with patients and their parents. During COVID-19 pandemic an online education improved patients' quality of life, which should be scrutinized as an important action in potential future crises [18].

Contrasting previously reported, our cases did not have more problems with physical functioning. Anyway, it is observed in our study that during COVID-19 pandemic, age have correlated with physical health in girls, which suggests that more attention should be paid to female students of higher grades.

The introduction of modern technologies in diabetes care, significantly improved metabolic control and QoL in patients with T1D, and it can concurrently reduce complaints about feeling "low" or "high", but it must become available even for patients in developing countries [19,20].

Almost two-thirds of cases in our study reported feeling weak during the month before the interview, but it is not clear if it is the consequence of their chronic disease or it is just a COVID-19 infection symptom, because of unknown COVID status.

One of the rare studies on QoL of children with T1D during COVID-19 pandemic-related lockdown, showed no significant differences in QoL in children and their parents reports comparing periods before and immediately after lockdown [21]. On the other hand, the adults with T1D, 18 months after SARS-CoV2 outbreak, reported worsened lifestyles; gaining weight and worsening quality of sleep [22]. Moreover, Welling et al. investigated the impact of COVID pandemic-related lockdown on eating behaviors, physical activity and QoL in children with severe obesity, and also observed deterioration [23].

Our study has few limitations. According to the lack of QoL assessment just before COVID-19 pandemic in our research, we are unable to appropriately conclude on the effects of pandemic. Having in mind that regular face-to-face check-ups were reduced, and people avoided visiting hospital, it might contribute to unsatisfying QoL scores in T1D patients. Our results would also be more accurate if data on participants' psychological evaluation were avaliable. It is also unknown if controls in our study had other acute or chronic disease at the moment of data gathering, neither their COVID-19 status.

5. Conclusions

Results of our study suggest that, as it was expected, there is a significant difference in QoL between children with T1D and their controls. The lowest QoL scores were observed in the domain of school functioning, in rural area, as well among boys with T1D and in the central region. Children with T1D were deeply concerned regarding their health which emphasizes the need for psychological support. During COVID-19 pandemic, age has correlated with physical health in girls, which suggests that more attention should be paid to female students of higher grades. It is good to be prepared for some future public crisis with an anticipated strong impact on public health, by conducting QoL studies and monitoring quality of life of children with T1D during crisis, because that is the only way to have timely reactions and prevent consequences. Like that, results of our current study provide insights to prioritizing actions for children with diabetes care as well as for public healthcare planning.

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Trends in nationwide incidence of pediatric type 1 diabetes in Montenegro during the last 30 years

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Significant and unexplained variations in type 1 diabetes (T1D) incidence through the years were observed all around the world. The update on this disorder's incidence is crucial for adequate healthcare resource planning and monitoring of the disease. The aim of this study was to give an update on the current incidence of pediatric T1D in Montenegro and to analyze incidence changes over time and how the exposure to different factors might have affected it. This retrospective cohort study included a total of 582 patients younger than 15 years who were newly diagnosed with T1D during the past 30 years. The average age at diagnosis was 8.4 ± 3.91 years. The mean annual incidence of T1D in the Montenegro population during the whole study period of 30 years was 15.2/100,000 person-years. Slightly higher incidence rates were observed in male compared to female individuals, and the incidence increased with age, with the highest incidence in the 10–14 age group. If the model is observed as one without jointpoints, the annual percentage change (APC) for the total population is 3.1 (1.8–4.4); for male individuals, 3.8 (2.1–5.5); and for female individuals, 2.1 (0.6–3.5). In 2020, the first year of the coronavirus disease of 2019 (COVID-19) pandemic, in comparison to 2019, the incidence rate increased from 19.7/100,000 to 21.5/100,000, with the highest increase in the age group of 5–9 years. This is the first nationwide report on a 30-year period of T1D incidence trend in Montenegro. It suggests that T1D incidence among Montenegrin children is rising again and that there is a short-term influence of COVID-19 on new-onset T1D.

KEYWORDS

diabetes mellitus, T1D, incidence, COVID19, Montenegro (Crna Gora)

Abbreviations: T1D, type 1 diabetes; EURODIAB, a collaboration of European Childhood Diabetes Registers; MODY, maturity onset diabetes of youth; APC, annual percentage change; COVID-19, coronavirus disease of 2019.

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Introduction

Significant and unexplained variations in type 1 diabetes (T1D) incidence through the years were observed all around the world. The update on T1D incidence is crucial for unexceptional healthcare resource planning and monitoring of this disease, which is still unpreventable and concerning. Moreover, the incidence of T1D shows an increasing trend in Europe, and it sharply increased since 2019 (1).

North European countries (Finland, Sweden, Norway, the United Kingdom, and Ireland) are at the top of the list among countries with the highest incidence of T1D (27.5–52.2/100,000), but the incidence is also very high in the Italian region of Sardinia (45.0/100,000), which is located in the south-western part of Europe (1, 2).

According to the last census (2011), Montenegro is a south-eastern European country, with an area of 13.812 km^2 and a population of 620.145, including 118,751 (19%) children younger than 15. Results of prior studies classified Montenegro as a country with a high incidence rate of T1D (18.5/100,000 for the period 2009–2013) (3, 4). However, the last report regarding the incidence of T1D was based on data from almost a decade ago, and analysis of more recent data is needed to gain insight into the current epidemiological situation regarding T1D in Montenegro.

The aim of this study was to give an update on the current incidence of pediatric T1D in Montenegro and to analyze incidence changes over time and how the exposure to different factors might have affected it, which should be useful for further projection of T1D prevalence.

Methods

The study included children younger than 15 years who were newly diagnosed with T1D during the period 1991–2020. The data source was the Diabetes Registry of Montenegro (established according to the EURODIAB Collaborative group propositions) and patients' medical records at the Institute for Children's Diseases, Clinical Center of Montenegro. The Institute for Children's Diseases is the referent diabetes center for Montenegro, the only center where the diagnosis of T1D could be made and where insulin therapy is initially started and prescribed. Study protocol was formally approved by the Ethics Committee of Clinical Center of Montenegro (no. 03/01-24708). Second data source were records from the Institute of Public Health of Montenegro, which provided capture–recapture methodology (5). Children with other types of diabetes, such as type 2 diabetes or maturity-onset diabetes of the youth (MODY) were excluded from the study. The population denominator data were obtained from the 1991, 2003, and 2011 national census data of the Central Bureau of Statistics (Monstat). Due to long intervals between national censuses, the estimated numbers of habitants were used in order to obtain the number of habitants for each year in the period between 2000 and 2020. In the period from 1991 to 1999, no estimates of population were found, and due to the fact that during these years, there was a conflict in the region and subsequently high population migration, modeling of data was used to obtain estimates of the population in this period. For that purpose, the polynomial regression analysis was used to fit the data and impute the missing values.

Collected variables included gender, date of birth, and date of the onset of T1D. Three types of incidence rates, expressed as new cases per 100,000 persons, were calculated: age specific, age standardized, and crude. Age-specific rates were adjusted to three age groups (0–4, 5–9, and 10–14). Age-adjusted incidence rates were calculated using Segi's World population (6).

The annual percentage change (APC), a number assumed as a constant percentage change of the previous year rate, was determined using jointpoint regression analysis. The joinpoint analysis was performed in Joinpoint Regression Program, v4.9.0.0, March 2021, Statistical Research and Applications Branch, National Cancer Institute.

Results

During the study period (1991–2020), there were a total of 582 children with newly diagnosed T1D, in which 317 were boys and 265 were girls. The average age at diagnosis was 8.4 ± 3.91 years. The mean annual incidence of T1D in the Montenegro population during the whole study period of 30 years was 15.2/100,000 person-years. The age- and sex-category-specific rates for the whole study period are shown in Table 1 and age-standardized incidence rate for 5-year period in Table 2.

Slightly higher incidence rates were observed in male compared to female patients (Figure 1). The incidence increased with age, with the highest incidence in the 10–14 age group (Figure 2). The same trend is observed in the gender stratum (Table 1).

If the model is observed as one without jointpoints, the APC for the total population is 3.1 (1.8–4.4); for male individuals, 3.8 (2.1–5.5); and for female individuals, 2.1 (0.6–3.5). However, in both genders model, one significant joinpoint was obtained; for the period 1991–1995, APC is 40.96, while in the period 1995–2020, APC is 20.06. In female individuals, there is one significant joinpoint as well, and the APC for the period 1991–1995 is 36.76, while for the period 1995–2020, APC is 1.07. Every segment is shown separately in Figure 3.

In 2020, the first year of the COVID-19 pandemic, in comparison to 2019, the incidence rate increased from 19.7/100,000 to 21.5/100,000, with the highest increase in the age

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TABLE 1 Number of cases, total person years, means annual incidence, age-specific incidence, and age-standardized incidence of T1D in Montenegro during the period 1991–2020.

	No. of cases	Total person years	Mean annual age spec. incidence (95% CI) per 100,000	Age stand. incidence per 100,000
Total				
All (0–14)	582	3,729,405	15.6 (1.44–4.69)	15.2
0–4	133	1,201,286	11.1 (0.93–1.31)	
5–9	214	1,223,417	17.5 (1.52–2.00)	
10–14	235	1,304,702	18.0 (1.58–2.05)	
Boys				
All (0–14)	317	1,933,557	16.4 (1.46–1.83)	15.9
0–4	70	625,164	11.2 (0.87–1.41)	
5–9	113	633,132	17.9 (1.47–2.15)	
10–14	134	675,261	19.8 (1.66–2.35)	
Girls				
All (0–14)	265	1,795,848	14.8 (1.30–1.66)	14.4
0–4	63	576,122	10.9 (0.84–1.39)	
5–9	101	590,285	17.1 (1.39–2.08)	
10–14	101	629,441	16.1 (1.31–1.95)	

group of 5–9 years (Table 3), with similar variations among age and gender groups also reported at different time points during the past three decades.

Discussion

The results of this nationwide epidemiological study in 0–14-year-old children showed that Montenegro is a country with a high incidence rate of T1D (in the range of 10–19.9/100.000) (7, 8).

The previous report on the incidence of T1D in Montenegro has been published by Patterson et al., in their multicentric study, and our results point out that the incidence is higher since then (3). If we observe only the last 15-year period, the incidence of T1D in Montenegro can be classified as very high in male individuals younger than 15 (21.6–22.7/100,000). Knowing the data on T1D incidence trend, in the whole 0–14-year-old population and also in different age subgroups, is very important for the monitoring of the disease and for adequate healthcare resource planning and distribution.

In comparison to neighboring countries, T1D incidence in Montenegro is similar to Serbia (14.3/100,000 for the period 2007–2017), Slovenia (16.3/100,000 for the period 2009–2013), and Croatia (17.2/100,000 for the period 2004–2012), but it is significantly higher than in a Former Yugoslavian Republic of Macedonia (7.7/100,000 for the period 2009–2013) and Bosnia and Herzegovina–Tuzla region (6.9/100,000 for the period 1990–1998), which have higher rates of incidence increase in the later period than in previous countries (possibly due to prior underreporting of T1D) (3, 9–11).

TABLE 2 Age-standardized incidence rates of T1D in children aged 0–14 in Montenegro—5-year periods compared.

Age std. inc. rate (per 100,000)	Total	Boys	Girls
1991–1995	7.6	7.1	8.12
1996–2000	12.1	12.1	12.1
2001–2005	14.8	11.4	18.5
2006–2010z	18.4	22.7	13.7
2011–2015	20.7	22.5	18.7
2016–2020	19.2	21.6	16.5
Whole period	15.2	15.9	14.4

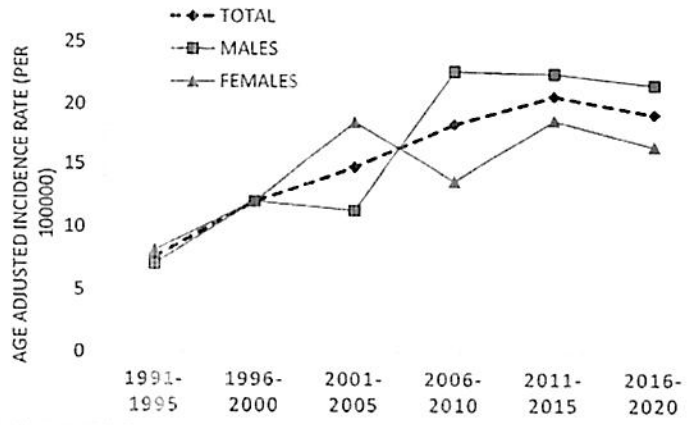

FIGURE 1
Trend of age-adjusted incidence rate (per 100,000), Montenegro, 1991–2020.

During the 30 years of follow-up, the incidence increased by approximately 3.1% annually, but in the last years, the increase appears to be slowing down. The suggested slowing in the period 2004–2008 and cyclical 5-year periodicity in incidence pattern were not observed in our country (3).

Similarly across Europe, T1D is predominantly diagnosed in children 10–14 years old, but the average age at the onset of the disease is a bit lower (3, 12, 13). It could be due to the high childhood obesity rate or lower immunization coverage rate, which will be discussed in the following text. Opposite to other studies, we did not observe the highest incidence rate increase in boys younger than 5, but it is less marked in girls aged 0–4 years than in other age/sex subgroups (3, 14). In 2020, the highest incidence rate increase was among 5–9 years old.

Significant variations in T1D incidence through the years are still unexplained. Although, genetics, lifestyle, and socioeconomic factors play important roles in the development of type 1 diabetes, a majority of studies suggest environmental factors as crucial (15–17). The emphasis is on the decrease in infectious diseases frequency, increase in vaccination coverage rate, and changes in the food and supplements intake.

According to the accelerator hypothesis, childhood obesity significantly impacts the development and incidence of all types of diabetes, including T1D (18). In both obesity and type 1 diabetes, leptin, resistin, and β-cell autoimmunity are elevated, but it is not clear yet if obesity accelerates or causes type 1 diabetes (19). It is known that, in 2013, every fourth Montenegrin school-aged child was overweight, and the number of overweight boys was twice

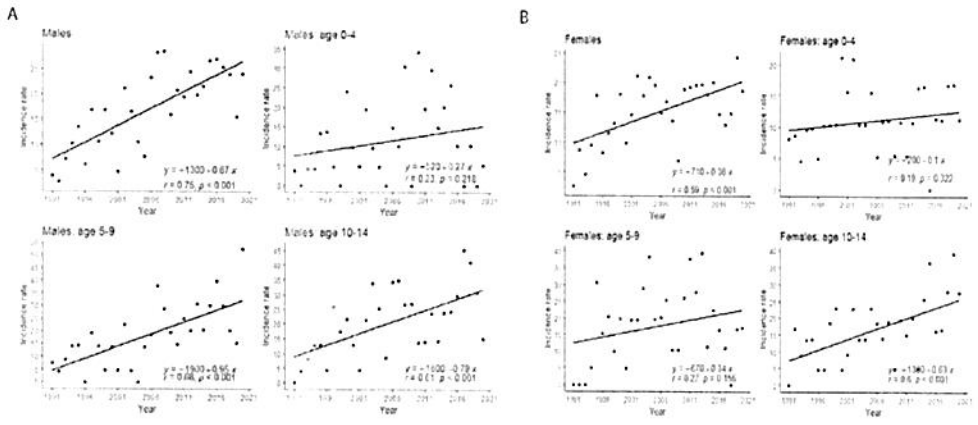

FIGURE 2
Trends of crude incidence rates of T1D in different age groups in (A) boys and (B) girls.

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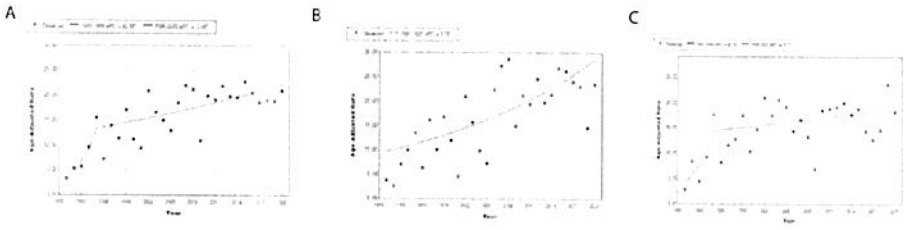

FIGURE 3
Jointpoint regression analysis: trend of standardized incidence rates of T1D in different gender groups, in (A) total, (B) boys, and (C) girls.

higher in comparison to girls (20). Since then, many inhabitants from the rural parts migrated to the urban parts of the country; a lot of people started a sedentary lifestyle with increased intake of high-calorie foods, which is expected to have led to even higher obesity rate and sustained increase in T1D incidence.

Like the rest of the world, Montenegro has been affected by the ongoing worldwide pandemic (COVID-19 pandemic) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus since its first case was confirmed on 17 March 2020. For more than 50 years, viruses are considered potential triggers for autoimmune diseases such as T1D (21, 22). Furthermore, some authors reported an increased incidence of new-onset T1D during the first year of the COVID-19 pandemic (23–25). SARS-CoV-2 tropism to pancreatic β cells is supposed to be due to their angiotensin-converting enzyme 2 (ACE2) receptors and neuropilin 1 (NRP1) receptors, and virus–receptor interactions lead to cell damage and impaired insulin secretion. Moreover, high blood glucose level "stimulates" replication of the virus and damage progress (26–28). Opposed to those findings and in line with our results, Mameli et al. have described the double wave occurrence, with the decrease in T1D incidence in the first wave of the COVID-19 pandemic, as also Kostopoulou reported (29, 30). It could be related to the fact that T1D is manifested a few months after a child's contact with the trigger, in this case, the SARS-CoV-2 virus. On the other hand, if we observe a pandemic and strict lockdown in the first months as a stress, which could also be a trigger for T1D development, the incidence increase could be registered earlier (31). The highest increase in incidence rate during the first year of COVID-19 was observed in children older than 5 but younger than 10, which was also described as a finding in the Italian region of Calabria (13).

Hence, a similar peak in incidence rate to the one in the first year of the COVID pandemic was observed in 2016 (Table 3), which could be due to a significantly decreased rate of immunization with measles–mumps–rubella (MMR) vaccine among Montenegrin children that year (2015—whole country coverage of 93.5%, 98% in the capital city; 2016—whole country coverage of 86.4%, 73.0% in the capital city; 2017—whole country coverage of 92.2%, 97.7% in the capital city) (32–35). In the following years, the government introduced mandatory immunization certificates for children who want to stay in kindergarten, which improved the immunization coverage rate.

The strength of this study is its nationwide character and timeliness with a long observational period of 30 years supported by the completeness of the diabetes registry and high-quality data from the second source. The limitation of the present study is a lack of the exact number of inhabitants in the period 1991–1999, which we assumed and predicted using the mathematical mode (polynomial regression).

This is the first nationwide report on a 30-year period of T1D incidence trend in Montenegro. It suggests that T1D incidence among Montenegrin children is rising again, after a plateau, and that there is a short-term influence of COVID-19

TABLE 3 Crude incidence rate of T1D in Montenegro for the last 5 years, in different age groups.

Age groups (years) Crude incidence rate(per 100,000 persons/year)	0–4	5–9	10–14	Total
2016	10.9	28.6	23.1	21.0
2017	5.4	21.0	31.6	19.4
2018	13.4	10.6	34.9	19.6
2019	8.1	16.0	34.9	19.7
2020	8.2	35.4	21.1	21.5

on new-onset T1D. The highest increase in the first year of the COVID pandemic is registered in 5–9-year-olds.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

MR, MS, and RV designed the research study. MR and NP gathered the data. IS conducted statistical analyses. MR and IS wrote the first draft of the manuscript. All authors contributed to study design and revised and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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