Symptoms and Glycemic Control in Young People With Type 1 Diabetes Following SARS-CoV-2 Infection: An Observational Study

Revital Nimri,[1,2] **Marianna Rachmiel,**[2,3] **Michal Yackobovitch-Gavan,**[1,2] **Avivit Brener,**[2,4]
Liat de Vries,[1,2] **Naama Fisch Shvalb,**[1,2] **Liora Lazar,**[1,2] **Asaf Oren,**[2,4] **Talia Jacobi-Polishook,**[3]
Noa Shefer Averbuch,[1,2] **Ariel Tenenbaum,**[1,2] **Eran Mel,**[1] **Sari Krepel Volsky,**[1,2] **Marie Mouler,**[1,2]
Sharon Demol,[1,2] **Shlomit Shalitin,**[1,2] **Rachel Bello,**[1,2] **Moshe Phillip,**[1,2] **and Yael Lebenthal**[2,4]

[1]The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva 49202, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, 69978, Israel
[3]Pediatric Endocrinology and Diabetes Institute, Shamir (Assaf Harofeh) Medical Center, Tzrifin,70300, Israel and
[4]Pediatric Endocrinology and Diabetes Unit, Dana-Dwek Childrens Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv,6423906, Israel
Correspondence: Revital Nimri, MD, The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, 14 Kaplan St, Petah Tikva, 49202, Israel. Email: Revitalnimri@gmail.com; Ravitaln@clalit.org.il.

Abstract

Context: Data is needed regarding the effect of SARS-CoV-19 infection on young people with established type 1 diabetes. Identifying the disease outcomes, short and long-term sequelae may help to establish an evidence-based prevention and education policy for sick days management and DKA prevention.

Objective: This work aims to describe clinical manifestations of SARS-CoV-2 infection in children, adolescents, and young adults with established type 1 diabetes (T1D) and explore the effects of COVID-19 on glycemic control and disease course.

Methods: An observational study was conducted at 3 pediatric diabetes clinics in Israel between mid-March 2020 and mid-March 2021. Included were young people with established T1D, age younger than 30 years, who tested positive for SARS-CoV-2 (quantitative real-time polymerase chain reaction). Data were collected from medical files, diabetes devices, and COVID-19 questionnaire. Outcome measures were analyzed by the presence/absence of clinical symptoms (symptomatic/asymptomatic) and by age group (pediatric, < 19 years/young adults, 19-30 years).

Results: Of 132 patients, mean age 16.9 ± 5.3 years, with COVID-19–confirmed infection, 103 (78%) had related symptoms; the most common were headaches, fatigue, fever, and loss of sense of smell. All had a mild disease course, but 4 required hospitalization and 2 cases were directly related to COVID-19 infection (pleuropneumonia in a patient with immunodeficiency syndrome, 1 case of diabetic ketoacidosis). Logistic regression analysis showed that age (odds ratio [OR] = 1.11; 95% CI, 1.01-1.23; *P* = .033), elevated glucose levels (OR = 5.23; 95% CI, 1.12-24.41; *P* = .035), and comorbidities (OR = 8.21; 95% CI, 1.00-67.51; *P* = .050) were positively associated with symptomatic infection. Persistent symptoms occurred in 16.5% of the cohort over a median of 6.7 months; age (OR = 1.14; 95% CI, 1.01-1.29; *P* = .030) and elevated glucose levels (OR = 3.42; 95% CI, 1.12-10.40; *P* = .031) were positively associated with persistent symptoms. Usually, no change was reported in glucose levels (64%) except for a temporary deterioration in glycemic control during the short infection period.

Conclusion: Young people with established T1D experience mild COVID-19 infection. Elevated glucose levels during COVID-19 infection and older age were associated with prolonged disease course.

Key Words: asymptomatic infection, COVID-19, SARS-CoV-2 infection, type 1 diabetes, pediatric, DKA

Abbreviations: CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; IQR, interquartile range; OR, odds ratio; RT-PCR, real-time polymerase chain reaction; SEP, socioeconomic position; T1D, type 1 diabetes; T2D, type 2 diabetes.

In March 2020, the World Health Organization declared COVID-19 a pandemic (1). At the onset, most countries recommended considering people with chronic medical conditions, such as diabetes (type 1 [T1D] and type 2 [T2D]), to be at increased risk from COVID-19. Diabetes was one of the most prominent and earliest recognizable risk factors for COVID-19 severe acute respiratory syndrome, along with older age, overweight, and hypertension (2, 3). In many countries, asymptomatic community testing for COVID-19 was limited, thus the vast majority of clinical data were generated from hospitalized or symptomatic cohorts. The data were mainly retrieved from hospitalized patients for whom diabetes was regarded as a single condition, combining T1D and T2D (4, 5). Among hospitalized children, reported risk factors were age and comorbid conditions, including diabetes (combined T1D and T2D) (6). Emerging data showed that T1D and T2D are both independently associated with increased risk for hospitalization, severe illness, and mortality from COVID-19

infection ([5], [7], [8]). Nevertheless, young people with T1D are poorly represented in these studies and information is lacking regarding related risks in this population. Little is known about community-infected people with T1D, and even less about children and young adults as these age groups are less affected by COVID-19. More information on risk factors and clinical outcomes is needed to understand and mitigate the effect of COVID-19 among young people with T1D. Prevalence of COVID-19 antibodies was found to be comparable in children and adults with and without T1D ([9]), suggesting that young people with T1D are not at increased risk for COVID-19 infection. Nevertheless, concern has been raised whether COVID-19 infection among children with established T1D leads to increased risk for severe disease.

Because the COVID-19 infection is a relatively new condition, scarce data exist regarding its effect on diabetes control and blood glucose levels during infections. A preliminary report of 33 patients with T1D and a mean age of 20.9 years showed that more than 50% reported hyperglycemia and nearly one-third experienced diabetic ketoacidosis (DKA) ([10]). A literature review of 21 articles showed similar findings, as people with preexisting T1D and COVID-19 infection often present with hyperglycemia and/or DKA ([11]).

We aimed to describe the clinical manifestations of SARS-CoV-2 infection in children, adolescents, and young adults with established T1D, and to explore the effects of COVID-19 infection on glycemic parameters, disease course, and outcomes.

Materials and Methods

This observational study included young people with confirmed T1D diagnosis, up to age 30 years, who presented at 3 academic diabetes clinics in Israel for routine diabetes care and were confirmed for SARS-CoV-2 infection between mid-March 2020 and mid-March 2021. The cohort included unvaccinated individuals because vaccination in Israel for people aged 16 to 18 years started in February 2021. The participating centers were Schneider Children's Medical Center of Israel (Petah Tikva), the largest pediatric diabetes center in Israel, following more than 1900 people with T1D, Dana-Dwek Children's Hospital in Sourasky Medical Center (Tel Aviv) following approximately 350 people with T1D, and Shamir (Assaf Harofeh) Medical Center (Zerifin) following 280 people with T1D. Institutional review board approval was granted by each individual institution as appropriate, with Schneider Children's Medical Center as the primary site (institutional review board of Rabin Medical Center, No. 0940-20-MRC). The data were handled in accordance with the principles of good clinical practice.

All study participants tested positive for COVID-19 through a molecular test by real-time polymerase chain reaction (RT-PCR) from samples collected from nasopharyngeal and throat swabs. SARS-CoV-2 testing was performed in accordance with Israel's policy for symptomatic cases and/or in cases of contact with a person with confirmed COVID-19 infection.

People with type 1 diabetes were classified as symptomatic COVID-19–infection if they exhibited any of the common symptom profiles as identified by the US Centers for Disease Control and Prevention, including fever, cough, shortness of breath, myalgia, runny nose, sore throat, headache, nausea or vomiting, abdominal pain, diarrhea, or any combination of these symptoms. The symptomatic group was stratified by age into the pediatric group (< 19 years) and young adult group (≥ 19 years). Persistent or long COVID was defined according to the UK National Institute for Health and Care Excellence when symptoms persisted for more than 4 weeks after onset of acute symptoms ([12]).

The data for the study outcomes evaluation were retrieved from multiple sources. Information regarding demographics and characteristics of the study cohort was retrieved from the participants' medical records. Symptoms of COVID-19 infection were documented by physicians during routine clinic visits or by phone using a structured questionnaire, as well as self-reported glucose level changes (individuals were asked if and how their glucose levels changed during COVID-19 infection). Data regarding glucose levels were collected from data uploads of various diabetes treatments related devices (sensors, glucometers, and insulin pumps). Continuous glucose monitoring (CGM) data were retrieved for three 2-week periods: before COVID-19 (2 weeks preceding start date of symptoms, or in asymptomatic cases on the confirmed positive test date); during COVID-19 infection (start of symptoms until resolution or in asymptomatic cases 2 weeks after date of confirmed test); and after COVID-19 recovery (2 weeks after symptoms resolution or in asymptomatic cases during weeks 3 and 4 after date of confirmed test). CGM metrics were compared for the 3 time periods. The information retrieved from the ambulatory glucose profile report included: mean glucose levels (mg/dL), glucose SD (mg/dL), coefficient of variance (CV%), percentage time CGM active, time-in-target range (70-180 mg/dL; 3.9-10 mmol/L), time in alert hypoglycemia (< 70 mg/dL; < 3.9 mmol/L), time in clinically significant hypoglycemia (< 54 mg/dL; < 3 mmol/L), time in hyperglycemia (> 180 mg/dL; > 10 mmol/L), and time in clinically significant hyperglycemia (> 250 mg/dL; > 13.3 mmol/L). These definitions are in accordance with the international consensus on CGM interpretation ([13]). CGM data were available for only part of the cohort because of a lack of available uploaded data at the data recording phase, or if technically not available (eg, not saved in the data management system).

The 3 largest populations in Israel are the general Jewish (67%), Ultra-Orthodox Jewish (12%), and Arab (21%, mainly Muslim including Bedouin, and Christian) groups ([14]). Socioeconomic position (SEP) by home address (SEP cluster and SEP index) was analyzed based on the Israel Central Bureau of Statistics' Characterization and Classification of Statistical Areas within Municipalities and Local Councils by the Socio-Economic Level of the Population ([15]). Residential SEP cluster, based on locality of residence, was coded on a 1 to 10 scale and grouped into low (1-4), medium (5-7), and high (8-10) categories. The SEP index is an adjusted calculation of 14 variables that measure social and economic levels in the domains of demographics, education, standard of living, and employment—ranging from the lowest (–2.797) to the highest (+2.590).

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 27 (SPSS Inc). Characteristics of the study cohort were described and stratified by occurrence or absence of COVID-19–related symptoms. In addition, the symptomatic cohort was described and stratified by age, the pediatric group including individuals aged up to 19 years and the young adult including individuals

aged 19 to 30 years. Data are expressed as mean ± SD for normally distributed variables, and median (interquartile range, IQR) for skewed variables. Variables were compared between groups using independent t tests (for normally distributed variables), the Mann-Whitney test (for skewed variables), and Pearson χ^2 test or Fisher exact test (for categorical variables). Multiple logistic regression analysis (forward) was performed to explore variables associated with elevation in glucose levels during COVID-19 infection, symptomatic COVID-19 infection, and persistent symptoms. In the logistic regression analysis, age was analyzed in years as a continuous variable. A P value of less than .05 was considered statistically significant.

Results

We identified 132 individuals with established T1D who tested positive for SARS-CoV-2 by RT-PCR method, of whom 88 (66%) were in the pediatric group and 45 (34%) in the young adult group. In 60% of cases, the cause for swab testing was contact with a COVID-19–positive person. The average age was 16.9 years (range, 0.6-30 years); 53% were female, and the median glycated hemoglobin A_{1c} (HbA_{1c}) was 7.7% mmol/mol (60.6 mmol/mol), ranging from 5.7% to 14% (38.8-129.5 mmol/mol). Average duration of total cohort follow-up was 4.6 ± 2.9 months (range, 0.1-11.7 months). Overall SEP by locality of residence was below average, median SEP cluster was 4 (IQR, 2-7), mean SEP index was –0.316 ± 1.091, and 53% belonged to the lowest SEP category.

Characteristics of the study cohort stratified by presence/absence of symptoms are presented in Table 1. Among the study cohort, 78% reported at least one symptom of COVID-19 and 22% were asymptomatic. The symptomatic group as compared to the asymptomatic group was characterized by older age (17.4 vs 14.9 years; P = .027), belonging to the general Jewish population (P = .046), and higher presence of comorbidities (29.1% vs 6.9%; P = .014). The most common comorbidities were celiac and thyroid autoimmune disease in 18 of 32 (56%) cases; other comorbidities were neurologic disease (16%), hyperlipidemia (9%), asthma and allergy (6%), anxiety and eating disorders (6%), biliary atresia (3%), and immune deficiency (3%). There was no significant difference in SEP cluster between symptomatic and asymptomatic groups.

Clinical Presentation of COVID-19 Infection

The median duration of symptoms among the group with symptomatic COVID-19 infection was 5 days (IQR, 2-10 days), with a significantly shorter disease duration among the pediatric group as compared to the young adult group (median 4 [IQR, 2-7] vs 7 [IQR 2.5-14.5] days, respectively; P = .011). The 4 most commonly reported symptoms were headaches, fatigue, fever, and loss of sense of smell (Table 2). In cases with reported fever, the median temperature was 38.5 °C (range, 37.9-39.7 °C). Respiratory symptoms occurred in 24.3% of the symptomatic cohort population, of whom 88% experienced shortness of breath, and only one needed supplemental oxygen. Of note, none of the cohort lost the ability to speak or move. Muscle pain, loss of sense of taste, loss of sense of smell, and prolonged symptoms were significantly more common among the young adult group as compared to the pediatric group (see Table 2).

Prolonged symptoms from SARS-CoV-2 infection (last follow-up visit) were observed among 16.5% of the symptomatic cohort population over a median duration of 6.7 months

(IQR, 2.5-7.5 months). The most common symptoms were loss of sense of smell and taste, headaches, fatigue, cough, and shortness of breath (see Table 2); other symptoms were palpitations, muscle pain, hair loss, anxiety, and dizziness.

Stepwise logistic regression analysis showed that age (each additional year in age increases by 1.1 times the likelihood of having symptomatic infection, odds ratio [OR] = 1.11; 95% CI, 1.01-1.23; P = .033), reported elevated glucose levels (individuals with elevated glucose levels during infection had 5.23 times the odds of symptomatic infection, OR = 5.23; 95% CI, 1.12-24.41; P = .035), and comorbidities (existence of comorbidities raises the odds of having symptomatic infection by 8.21 times, OR = 8.21; 95% CI, 1.00-67.51; P = .050) were positively associated with symptomatic COVID-19 infection; no associations were found for population group, SEP index, or obesity. Stepwise logistic regression analysis showed that age (each additional year in age increases by 1.4 times the likelihood to have persistent COVID-19 symptoms, OR = 1.14; 95% CI, 1.01-1.29; P = .030) and reported elevated glucose levels (individuals with elevated glucose levels during infection had 3.42 times the odds of COVID-19 symptoms, OR = 3.42; 95% CI, 1.12-10.40; P = .031) were positively associated with persistent COVID-19 symptoms; no associations were found for population group, SEP index, obesity, or comorbidities.

Hospitalization Due to COVID-19

In the reported cohort, 4 (3%) young people with established T1D were hospitalized for 2 to 5 days (Table 3). All had a history of poor diabetes control, did not require respiratory support, and were discharged without complications. Case 1, a 17-year-old boy with X-linked agammaglobulinemia, was admitted because of pleuropneumonia with pleural effusion. He was treated with COVID-19 antibodies (from plasma of recovering people), steroids, and antibiotics with no need for supplemental oxygen therapy or other respiratory support. He was discharged after 5 days' hospitalization without any sequelae. The other 3 individuals had mild COVID-19 infection: Two were hospitalized for observation and one because of DKA (tested positive for COVID-19 at admission).

Glycemic Control and COVID-19 Infection

Most (64%) people reported no change in glucose levels during COVID-19 infection. Approximately one-third reported elevated blood glucose; around 5% reported experiencing low blood glucose; and 2% a combination of low and elevated blood glucose. People with symptomatic COVID-19 infection more frequently reported changes in glucose levels as compared to those who were asymptomatic (41.7% and 9.1%, respectively; P = .039), with no differences between age groups.

During the COVID-19 infection 76 of 132 (57.6%) of the cohort population used CGM. Data for the 3 periods assessed (before, during, and after the COVID-19 infection) were available for 36 (47.4%) of the CGM users (Fig. 1). Mean age of the reported CGM users was 15.6 ± 5.7 years, 14 (38.9%) were male, and 31 (86.1%) were symptomatic, of whom 11 (30.6%) had a fever. Average sensor glucose levels during COVID-19 infection were significantly higher than post infection (169.4 ± 30.6 mg/dL vs 161.6 ± 27.6 md/dL, respectively; P = .01). The percentage of time spent above range (> 180 mg/dL) significantly increased (from 32.2 ± 16.3% to 36.1 ± 17.2%; P = .038) and the percentage

Table 1. Clinical characteristics of symptomatic and asymptomatic young people with established type 1 diabetes and COVID-19

	Overall n = 132	Symptomatic COVID-19 n = 103 (78%)	Asymptomatic COVID-19 n = 29 (22%)	P
Age, y	16.9 ± 5.3	17.4 ± 5.0	14.9 ± 5.9	**.027**
Age categories, n (%)				
Pediatric group < 19 y	87 (65.9)	65 (63.1)	22 (75.9)	.201
Young adult group ≥ 19 y	45 (34.1)	38 (36.9)	7 (24.1)	
Female sex, n (%)	71 (53.8)	59 (57.3)	12 (41.4)	.129
Duration of diabetes, y	7.8 ± 5.3	8.1 ± 5.4	6.5 ± 4.9	.700
Population groups, n (%)				
General Jewish	72 (54.5)	62 (60.2)	10 (34.5)	**.046**
Ultra-Orthodox Jewish	47 (35.6)	31 (30.1)	16 (55.2)	
Arab Muslim/Christian	10 (7.6)	8 (7.8)	2 (6.9)	
Others	3 (2.3)	2 (1.9)	1 (3.4)	
Socioeconomic position categories, n (%)				
Low, 1-4	70 (53.0)	50 (48.5)	20 (69.0)	.149
Medium, 5-7	47 (35.6)	40 (38.8)	7 (24.1)	
High, 8-10	15 (11.4)	13 (12.6)	2 (6.9)	
Socioeconomic position, index	−0.316 ± 1.091	−0.207 ± 1.078	−0.668 ± 1.078	**.040**
People aged < 19 y Body mass index, z scores	n = 86 0.44 ± 1.68	n = 64 0.57 ± 1.45	n = 21 0.14 ± 2.27	.422
People aged ≥ 19 y Body mass index	n = 45 24.5 ± 4.08	n = 38 24.4 ± 4.05	n = 7 25.3 ± 4.48	.595
Obesity, body mass index z score ≥ 2 SDS	14 (10.6)	11 (10.7)	3 (10.3)	.992
Mode of insulin delivery, n (%)				
Insulin pump	86 (65.2)	67 (65)	19 (65.5)	.829
Multiple daily injections	43 (32.6)	33 (32)	10 (34.5)	
Basal insulin and insulin pump	2 (1.5)	2 (1.9)	0	
Automated insulin delivery	1 (0.8)	1 (1)	0	
Continuous glucose monitoring use, n (%)	97 (73.5)	72 (69.9)	25 (86.2)	.182
Episodes of DKA, per 1000 person-y	7.8	8.7	5.5	.999
HbA$_{1c}$ nearest infection				
%	7.7 (7.1-8.8)	7.7 (7.1-8.8)	7.5 (7.0-9.2)	.893
mmol/mol	60.6 (54.1-72.7)	60.6 (54.1-72.7)	58.5 (53-77)	
HbA$_{1c}$ categories, %	n = 115	n = 91	n = 24	.976
< 7	24 (20.9)	18 (19.8)	6 (25)	
7-7.9	49 (42.6)	39 (42.9)	10 (41.7)	
8-8.9	31 (27)	25 (27.5)	6 (25)	
9-9.9	10 (8.7)	8 (8.8)	2 (8.3)	
≥ 10	1 (0.9)	1 (1.1)	0	
Comorbidities	32 (24.2)	30 (29.1)	2 (6.9)	**.014**
Reason for qRT-PCR swab test				
Contact with COVID-19–positive person	80 (60.6)	52 (50.5)	28 (96.6)	**< .001**
Symptoms	25 (18.9)	25 (24.3)	0	
Contact and symptoms	25 (18.9)	25 (24.3)	0	
Screening	2 (1.5)	1 (1)	1 (3.4)	
Self-reported glucose level changes	n = 125	n = 103	n = 22	**.039**
No change	80 (64)	60 (58.3)	20 (90.9)	
Elevated	36 (28.8)	34 (33)	2 (9.1)	
Low	6 (4.8)	6 (5.8)	0	
Elevated and low	3 (2.4)	3 (2.9)	0	

Data are presented as mean ± SD, median (interquartile range), and number (percentage). Bold values denote statistical significance at the P less than .05 level.
Abbreviations: DKA, diabetic ketoacidosis; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; qRT-PCR, quantitative real-time polymerase chain reaction.

Table 2. COVID-19 symptoms among young people with established type 1 diabetes

	Overall n = 103	Pediatric group Age < 19 y n = 65	Young adult Age ≥ 19 y n = 38	P
Duration of symptoms—median (IQR), d	5 (2-10)	4 (2-7)	7 (2.5-14.5)	**.011**
Headaches—n (%)	75 (72.8)	49 (75.4)	26 (68.4)	.443
Fatigue—n (%)	60 (58.3)	36 (55.4)	24 (63.2)	.440
Fever—n (%)	44 (42.7)	26 (40)	18 (47.4)	.466
Temperature—median (IQR), °C	38.5 (38-39)	38.5 (38-39)	38.5 (38-38.9)	.999
Myalgia—n (%)	33 (32)	15 (23.1)	18 (47.4)	**.011**
Sore throat—n (%)	32 (31.1)	18 (27.7)	14 (36.8)	.333
Cough—n (%)	16 (18.6)	9 (13.8)	7 (18.4)	.624
Rhinorrhea—n (%)	13 (15.1)	9 (13.8)	4 (10.5)	.541
Abdominal pain—n (%)	11 (10.7)	8 (12.3)	3 (7.9)	.484
Diarrhea—n (%)	6 (5.8)	2 (3.1)	4 (10.5)	.190
Vomiting—n (%)	3 (2.9)	2 (3.1)	1 (2.6)	.897
Skin rash—n (%)	2 (1.9)	2 (3.1)	0	.530
Respiratory distress—n (%)	25 (24.3)	15 (23.1)	10 (26.3)	.711
Shortness of breath	24 (21.4)	14 (21.2)	10 (26.3)	.609
Required supplemental oxygen	1 (1)	1 (2.6)	0	.999
Chest pain/pressure—n (%)	4 (3.9)	1 (1.5)	3 (7.9)	.294
Loss of smell—n (%)	44 (42.7)	22 (33.8)	22 (57.9)	**.017**
Loss of taste—n (%)	38 (36.9)	19 (29.2)	19 (50)	**.035**
Hospitalization—n (%)	4 (3.9)	2 (3.1)	2 (5.3)	.625
Self-reported glucose levels				
No change	60 (58.3)	36 (55)	24 (63.2)	.701
Elevated	34 (33)	22 (33.8)	12 (31.6)	
Low	6 (5.8)	4 (6.2)	2 (5.3)	
Elevated and low	3 (2.9)	3 (4.6)	0	
Persistent COVID-19 symptoms—n (%)	17 (16.5)	6 (9.2)	11 (28.9)	**.009**
Time elapsed from SARS-CoV-2 infection and last follow-up, mo	6.1 ± 3	5.6 ± 4.2	6.4 ± 2.6	.866
Most common:				
Loss of smell	7 (41.2)	2 (33.3)	5 (45.5)	
Fatigue	3 (17.6)	1 (16.7)	2 (18.2)	
Headaches	2 (11.8)	0	2 (18.2)	
Loss of sense of test	2 (11.8)	0	2 (18.2)	
Cough	2 (11.8)	1 (16.7)	1 (9.1)	
Shortness of breath	2 (11.8)	2 (33.3)	0	

Data are presented as number (percentage), median (interquartile range; IQR), and mean ± SD. Bold values denote statistical significance at the *P* less than .05 level.

Table 3. Characteristics of people with type 1 diabetes hospitalized due to COVID-19 infection

No.	Age, y	Sex	HbA$_{1c}$, %	Comorbidity	Reason for hospitalization	Treatment	Duration, d
1	17	M	10.1	X-linked agammaglobulinemia	Pleuropneumonia with pleural effusion	COVID-19 Ab, steroids, antibiotics	5
2	24	M	8.9	None	Rule out a cardiac event due to chest pain	Observation	2
3	14	F	10.6	None	Dyspnea and anxiety	Observation	3
4	22.5	F	9.6	None	Diabetic ketoacidosis	Fluids and insulin per DKA protocol	3

Abbreviations: Ab, antibodies; DKA, , diabetic ketoacidosis; F, female; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; M, male.
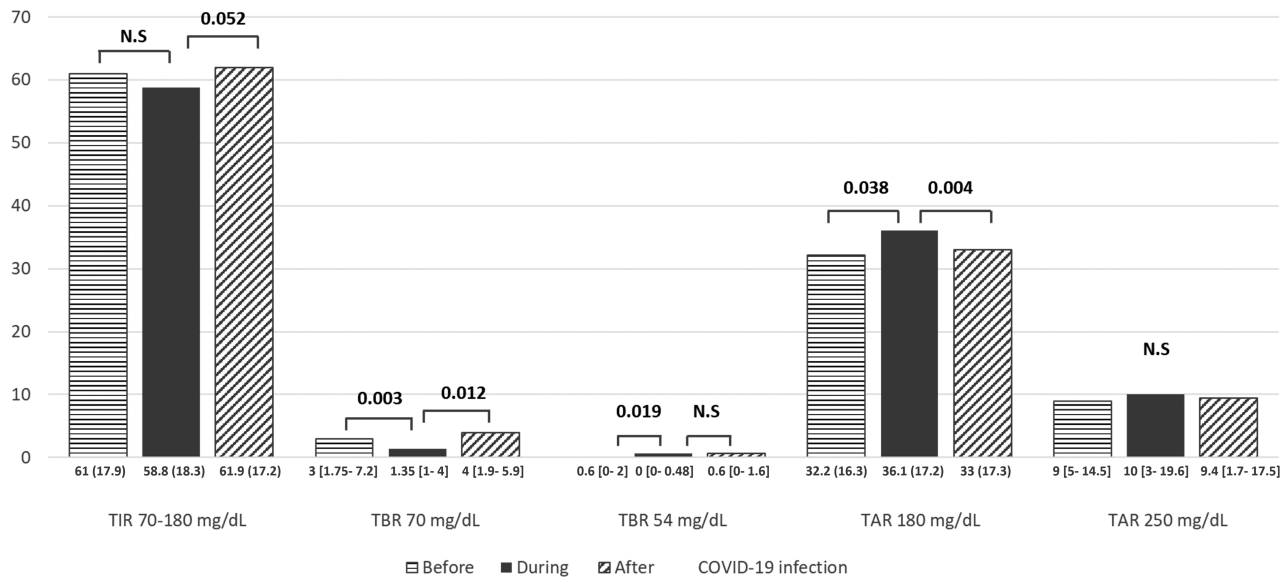
Figure 1. Continuous glucose monitoring time in ranges (%) 2 weeks before, during, and after COVID-19 infection (n = 36). Below each column, data for the percentage time in range are presented as mean (SD) or median (interquartile range) as appropriate.

of time spent below the range of 70 and 54 mg/dL significantly decreased (from 3.0% [1.75%-7.2%] to 1.35% [1%-4%]; $P = .003$ and from 0.6% [0%-2.0%] to 0% [0%-0.48%]; $P = .019$, respectively) during COVID-19 infection as compared to the period before. No significant change was found for percent time spent in range (70-180 mg/dL) (from 61.0% ± 17.9 to 58.8% ± 18.3; $P = .213$) and percent spent in clinically significant hyperglycemia (> 250 mg/dL) (from 9.0% [5.0-14.5] to 10.0% [3.0-19.6]; $P = .673$). After the COVID-19 infection, sensor glucose levels returned to the pre–COVID-19 infection levels (see Fig. 1). The percentage of time spent above range (> 180 mg/dL) significantly decreased (from 36.1% ± 17.2% to 33% ± 17.2%, $P = .004$) and the percentage of time spent below range (< 70 mg/dL) significantly increased (from 1.35% [1%-4%] to 4% [1.9%-5.9%]; $P = .012$) after COVID-19 infection.

In the logistic regression analysis, no variable (age, race/ethnicity, body mass index–SD score, diabetes duration, insulin delivery, CGM use, HbA_{1c}, and comorbidities) predicted elevation in glucose levels during COVID-19 infection.

No significant changes were found in measured HbA_{1c} pre infection, post infection, and at last follow-up visit for the entire cohort (median and IQR, 7.7% [7.1%-8.8%], 7.7% [7.1%-8.0%], and 7.8% [7.0%-8.7%], respectively); no changes in HbA_{1c} were found between the symptomatic and asymptomatic groups.

Discussion

In this observational study of 132 children, adolescents, and young adults with established T1D, who had COVID-19 infection, we found approximately one-quarter were asymptomatic and the remainder presented with a mild, short duration of symptomatic illness. Only 4 (3%) individuals required hospitalization, of whom 2 were directly related to the COVID-19 infection (1 case of pleuropneumonia in a patient with immunodeficiency syndrome and 1 case of DKA). The 2 other cases were hospitalized for observation, probably related to worry about health and fear COVID-19 infection.

This reflects the need for recognition and mental health support for youth diagnosed with COVID-19. Noteworthy, all hospitalized patients had poor glycemic control.

Our findings support the preliminary data (10) and a recently published study by Cardona-Hernandez et al (16), which showed that young people with T1D are not at increased risk of COVID-19 infection or for hospitalization. In contrast, Kompaniyets et al (17) reported that children with T1D had a higher risk of hospitalization and more severe illness when hospitalized. Nevertheless, their conclusions should be interpreted with caution because their cross-sectional study design could not establish causality. Their higher demonstrated risk for hospitalization might be related to the fact that more children with new-onset diabetes presented with DKA during a COVID-19 outbreak (18-20), therefore increasing the prevalence of hospitalization. It is important to emphasize in this context that our study included only individuals with established T1D. Furthermore, a study by Alonso and colleagues (21) showed that the primary cause for hospitalization of pediatric patients with established T1D and COVID-19 infection was DKA with poor glycemic control. These data from the US T1D Exchange registry showed that 61 of 266 people younger than 19 years with established T1D and COVID-19 infection were hospitalized. DKA was the most common adverse event in 72% of hospitalized cases. Another cohort from the United States including 1849 hospitalized people with T1D (mostly adults), found that the higher risk of intensive care unit admission was largely accounted for by the presence of DKA. After adjustment for DKA, people with T1D were not at increased risk for intensive care unit admission and had lower mortality rates compared to people with T2D (22).

Our data show that young people with T1D and COVID-19 infection exhibit a similar disease pattern as the general pediatric population. Studies report a range of 16% to 35% asymptomatic cases among the pediatric age group (23), similar to the 26% rate found in our study. The most common symptoms reported by our cohort were headache (73%), fatigue (58%), and fever (43%). These frequently observed symptoms are similar to those experienced by the general

pediatric population (24, 25). In most general children populations affected by COVID-19 the disease course is mild, short term, and rarely requires hospitalization (26). Similar to our findings, in most cases illness duration lasted 4 to 6 days and longer duration was associated with older children (25, 27). COVID-19 disease severity was found to be age related, with increased severity at extremely young age (< 3 months) or above 20 years, with comorbidities such as asthma and gastrointestinal conditions (6), and in adulthood above age 40 in an age-dependent manner (28). In a study of adults with T1D, only 0.2% of people were hospitalized with COVID-19 infection, similar to the rate of hospitalization in the general population (29). Those who were hospitalized were older than those who were not. Interestingly no differences were found in terms of glycemic control and comorbidity profile.

Although the entire cohort had mild COVID-19 infection, there was an age-related difference. We found that young adults with T1D and those with comorbidities were more likely to present with symptomatic COVID-19 infection. Symptomatic infection was not related to sex, level of diabetes control, duration of diabetes, treatment type, or body weight. In addition, older age was also a determinant for a longer duration of symptoms and young adults were more prone to long-term COVID-19 symptoms. A study that reported on 1-month follow-up reported that children had significantly shorter disease duration as compared to adults (30). Thus, young people with established T1D as compared to adults are not at increased risk for COVID-19 disease or hospitalization. At least part of these age-related differences stem from the increased rate of comorbidities in adults as compared to children, and a greater tendency to develop infections with age (31, 32).

Most patients did not experience a change in glucose levels during COVID-19 infection. Glucose levels were not affected in almost all cases of asymptomatic COVID-19 infection and most symptomatic cases. In approximately one-quarter of the cohort population that had available CGM data, a temporary deterioration in glycemic control was observed during the short infection period. Increased time in hyperglycemia and a trend of reduced time-in-target range were more frequently observed but some individuals also had more hypoglycemia events. This temporary short-term deterioration in glycemic control was more frequent among individuals with symptomatic COVID-19 infection. Blood glucose levels were restored in a fairly short time to previous levels, coinciding with the end of the viral infection. A similar observation was reported among 32 adults with T1D during the infection period (33). Thus, COVID-19 infection among young people with T1D probably resembles the effects of other viral infections during sick days (34). Our data add to the cumulative evidence that COVID-19 infection in youth with T1D does not increase the risk of developing DKA more than other infectious diseases. The occurrence of DKA is probably avoidable if sick day management guidelines are followed (35), emphasizing the need for reeducation and review of the guidelines for sick day management among youth during clinical visits, telemedicine, and through media. People with T1D and poor glycemic control are more prone to develop DKA during infection (36, 37) and therefore a higher rate of infection-related complications and hospitalization. Factors associated with worsening of blood glucose during COVID-19 infection were not found. A plausible explanation for the observed elevated glucose levels could be the stress response associated with the COVID-19 viral infection. In some other cases, lower glucose levels were observed, perhaps related to reduced appetite and gastrointestinal symptoms similarly to other infectious diseases. No changes were observed during follow-up between preinfection HbA_{1c} and last follow-up, implying that COVID-19 infection has no long-term sequelae on glucose metabolism.

As the world is still struggling with the pandemic, it is most important to identify the populations at risk that need to be targeted for early treatment and prevention strategies. Our study demonstrates that young people with established T1D are not at increased risk for severe COVID-19 disease or hospitalization; their main cause for hospitalization is DKA. Risk factors for hospitalization due to COVID-19 infection are similar to risk factors for DKA. Indeed, a higher rate of hospitalization was reported for those with poor glycemic control (21) and minorities such as non-Hispanic Black individuals (38), as these populations are more prone to develop any virus-induced DKA. Thus, education should focus on sick day management and DKA prevention during infectious disease, besides emphasizing the importance of achieving and maintaining good glycemic control. The data also suggest that those with comorbidities are more prone to developing symptomatic COVID-19 infection. This should be further investigated. Nevertheless, it is important to emphasize that morbidity and mortality from COVID-19 in children and young adults do exist even without comorbidities (39).

Our study has several limitations. First, the study design did not enable us to determine the prevalence of COVID-19 infection among young people with T1D followed at our academic centers. Although efforts were made to collect and document all cases of COVID-19 infection, some might have been missed. Second, the observational design of the study does not enable us to conclude on the relationship between COVID-19 exposure and outcome. Third, self-reported information on clinical symptoms could potentially introduce bias. Fourth, CGM data during COVID-19 infection was available for only a subset of participants. Fifth, the small number of hospitalized young people with T1D limits the ability of this study to assess who is at risk for hospitalization.

The presented study has several strengths. This is a relatively large and comprehensive population of young people with established T1D and confirmed COVID-19 infection followed at 3 ambulatory diabetes clinics. The study included only people with T1D. In addition, longitudinal data were gathered during routine visits. Longitudinal follow-up enables evaluation of the course and prolonged symptoms of COVID-19 infection among this population. Another strength is the ability to report on asymptomatic cases. This is thanks to easy access to COVID-19 testing shortly after the onset of the pandemic. In our cohort, 80 participants were tested because of contact with a person with COVID-19, of whom 35% were eventually found to be asymptomatic. Our finding of asymptomatic rate of infection is similar to the published meta-analysis estimation of 28% to 31% asymptomatic infection risk (40).

In summary, our findings suggest that young people with T1D, in most cases, experience a mild COVID-19 infection similar to the general pediatric population. Young adults with T1D are more prone to symptomatic disease and persistent symptoms. Long-term sequelae of COVID-19 in the pediatric age group have been recognized but further studies should describe the outcomes in future years. Therefore, precaution

measures and vaccination should be encouraged for all youth, including those with T1D.

Author Contributions

R.N., Y.L., M.R., and M.P. contributed to the study concept and design. R.N., Y.L., and M.R. are guarantors of this work, had full access to the study data, and are responsible for the integrity of the data and accuracy of the data analysis. R.N. wrote the first draft of the manuscript. All authors except M.Y.G. collected the data, participated in data analysis, and interpretation, and reviewed, edited, and approved the final version of the manuscript. M.Y.G. participated in data analysis and interpretation, statistical analysis, and reviewed and edited the manuscript.

Disclosures

The authors have nothing to disclose.

Data Availability

Data sets generated during and/or analyzed during the present study are not publicly available but can be made available from the corresponding author on reasonable request.

References

1. World Health Organization. *WHO Director-General's opening remarks at the media briefing on COVID-19*. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
2. Holman N, Knighton P, Kar P, *et al*. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol*. 2020;8(10):823-833.
3. Guo T, Shen Q, Ouyang X, *et al*. Clinical findings in diabetes mellitus patients with COVID-19. *J Diabetes Res* 2021;2021:7830136.
4. Grasselli G, Zangrillo A, Zanella A, *et al;* COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA*. 2020;323(16):1574-1581.
5. Hartmann-Boyce J, Rees K, Perring JC, *et al*. Risks of and from SARS-CoV-2 infection and COVID-19 in people with diabetes: a systematic review of reviews. *Diabetes Care*. 2021;44(12):2790-2811.
6. Graff K, Smith C, Silveira L, *et al*. Risk factors for severe COVID-19 in children. *Pediatr Infect Dis J*. 2021;40(4):e137-e145.
7. Barron E, Bakhai C, Kar P, *et al*. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol*. 2020;8(10):813-822.
8. Gregory JM, Slaughter JC, Duffus SH, *et al*. COVID-19 severity is tripled in the diabetes community: a prospective analysis of the pandemic's impact in type 1 and type 2 diabetes. *Diabetes Care*. 2021;44(2):526-532.
9. Jia X, Gesualdo P, Geno Rasmussen C, *et al*. Prevalence of SARS-CoV-2 antibodies in children and adults with type 1 diabetes. *Diabetes Technol Ther*. 2021;23(7):517-521.
10. Ebekozien OA, Noor N, Gallagher MP, Alonso G. Type 1 diabetes and COVID-19: preliminary findings from a multicenter surveillance study in the U.S. *Diabetes Care*. 2020;43(8):e83-e85.
11. Chang DJ, Moin T. Coronavirus disease 2019 and type 1 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes*. 2021;28(1):35-42.
12. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of Covid-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ*. 2021;372:n136.
13. Battelino T, Danne T, Bergenstal RM, *et al*. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42(8):1593-1603.
14. State of Israel. Central Bureau of Statistics. *Annual statistics of Israel, 2015*. Accessed Sep 11, 2021. https://www.cbs.gov.il/he/publications/Pages/2015/66.
15. State of Israel. Central Bureau of Statistics. Characterization and classification of geographical units by the socio-economic level of the population, 2015. Accessed October 2021. https://www.cbs.gov.il/he/publications/DocLib/2019/1765_socio_economic_2015/e_print.pdf
16. Cardona-Hernandez R, Cherubini V, Iafusco D, Schiaffini R, Luo X, Maahs DM. Children and youth with diabetes are not at increased risk for hospitalization due to COVID 19. *Pediatr Diabetes*. 2021;22(2):202-206.
17. Kompaniyets L, Agathis NT, Nelson JM, *et al*. Underlying medical conditions associated with severe COVID-19 illness among children. *JAMA Netw Open*. 2021;4(6):e2111182.
18. Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A; Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? *Diabetes Care*. 2020;43(11):2870-2872.
19. Unsworth R, Wallace S, Oliver NS, *et al*. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K. *Diabetes Care*. 2020;43(11):e170-e171.
20. Kamrath C, Mönkemöller K, Biester T, *et al*. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. *JAMA*. 2020;324(8):801-804.
21. Alonso GT, Ebekozien O, Gallagher MP, *et al*. Diabetic ketoacidosis drives COVID-19 related hospitalizations in children with type 1 diabetes. *J Diabetes*. 2021;13(8):681-687.
22. Barrett CE, Park J, Kompaniyets L, *et al*. Intensive care unit admission, mechanical ventilation, and mortality among patients with type 1 diabetes hospitalized for COVID-19 in the U.S. *Diabetes Care*. 2021;44(8):1788-1796.
23. Nikolopoulou GB, Maltezou HC. COVID-19 in children: where do we stand? *Arch Med Res*. 2022;53(1):1-8.
24. Mantovani A, Rinaldi E, Zusi C, Beatrice G, Saccomani MD, Dalbeni A. Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis. *Pediatr Res*. 2021;89(4):733-737.
25. Howard LM, Garguilo K, Gillon J, *et al*. The first 1000 symptomatic pediatric SARS-CoV-2 infections in an integrated health care system: a prospective cohort study. *BMC Pediatr*. 2021;21(1):403.
26. Dong Y, Mo X, Hu Y, *et al*. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145(6):e20200702.

27. Molteni E, Sudre CH, Canas LS, *et al*. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. *Lancet Child Adolesc Health*. 2021;5(10):708-718.

28. Demeterco-Berggren C, Ebekozien O, Rompicherla S, *et al*. Age and hospitalization risk in people with type 1 diabetes and COVID-19: data from the T1D Exchange Surveillance Study. *J Clin Endocrinol Metab*. 2022;107(2):410-418.

29. Vangoitsenhoven R, Martens PJ, van Nes F, *et al*. No evidence of increased hospitalization rate for COVID-19 in community-dwelling patients with type 1 diabetes. *Diabetes Care*. 2020;43(10):e118-e119.

30. Mizrahi B, Shilo S, Rossman H, *et al*. Longitudinal symptom dynamics of COVID-19 infection. *Nat Commun*. 2020;11(1):6208.

31. Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. *Diabetes Care*. 2018;41(3):513-521.

32. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. *Diabetes Care*. 2018;41(10):2127-2135.

33. Longo M, Scappaticcio L, Petrizzo M, *et al*. Glucose control in home-isolated adults with type 1 diabetes affected by COVID-19 using continuous glucose monitoring. *J Endocrinol Invest*. 2022;45(2):445-452.

34. Laffel LM, Limbert C, Phelan H, Virmani A, Wood J, Hofer SE. ISPAD Clinical Practice Consensus Guidelines 2018: sick day management in children and adolescents with diabetes. *Pediatr Diabetes*. 2018;19(Suppl 27):193-204.

35. Priyambada L, Wolfsdorf JI, Brink SJ, *et al*. ISPAD Clinical Practice Consensus Guideline: diabetic ketoacidosis in the time of COVID-19 and resource-limited settings-role of subcutaneous insulin. *Pediatr Diabetes*. 2020;21(8):1394-1402.

36. Pettus JH, Zhou FL, Shepherd L, *et al*. Incidences of severe hypoglycemia and diabetic ketoacidosis and prevalence of microvascular complications stratified by age and glycemic control in U.S. adult patients with type 1 diabetes: a real-world study. *Diabetes Care*. 2019;42(12):2220-2227.

37. Maahs DM, Hermann JM, Holman N, *et al*; National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health, the DPV Initiative, and the T1D Exchange Clinic Network. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. *Diabetes Care*. 2015;38(10):1876-1882.

38. Ebekozien O, Agarwal S, Noor N, *et al*. Inequities in diabetic ketoacidosis among patients with type 1 diabetes and COVID-19: data from 52 US clinical centers. *J Clin Endocrinol Metab*. 2021;106(4):e1755-e1762.

39. Feldstein LR, Rose EB, Horwitz SM, *et al*; *Overcoming COVID-19 Investigators; CDC COVID-19 Response Team*. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383(4):334-346.

40. Alene M, Yismaw L, Assemie MA, *et al*. Magnitude of asymptomatic COVID-19 cases throughout the course of infection: a systematic review and meta-analysis. *PLoS One*. 2021;16(3): e0249090.