



# Clinical characteristics and outcomes of COVID-19 in children and adolescents with diabetes in Daegu, South Korea

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**Purpose:** Children with comorbidities have a higher risk of severe, coronavirus disease 2019 (COVID-19). This study investigated the clinical features and outcomes of COVID-19 in children and adolescents with diabetes between January and March 2022.

**Methods:** We retrospectively reviewed the medical records of 123 children and adolescents (73 with type 1 diabetes and 50 with type 2 diabetes, 59 males and 64 females) aged <18 years who had been diagnosed with diabetes. Data were collected from 7 academic medical centers in Daegu, South Korea.

**Results:** Thirty-five children with diabetes were diagnosed with COVID-19 (18 with type 1 and 17 with type 2 diabetes). Eighteen of the 35 children with diabetes and COVID-19 and 50 of the 88 children with diabetes alone received a COVID-19 vaccination. No significant differences were observed between patients with diabetes and COVID-19 and patients with diabetes alone in the type of diabetes diagnosed, sex, age, body mass index, hemoglobin A1c, or vaccination status. All children with diabetes and COVID-19 had mild clinical features and were safely managed in their homes. Fourteen children had a fever of 38°C or higher that lasted for more than 2 days, 11 of whom were not vaccinated ( $P=0.004$ ). None experienced post-COVID-19 conditions.

**Conclusion:** All children and adolescents with pre-existing diabetes had mild symptoms of COVID-19 due to low disease severity, high vaccination rates, uninterrupted access to medical care, and continuous glucose monitoring. Unvaccinated children with diabetes who experienced COVID-19 presented with higher and more frequent fevers compared to vaccinated children.

**Keywords:** COVID-19, SARS-CoV-2, Diabetes mellitus

## Highlights

- All children and adolescents with pre-existing diabetes, coronavirus disease 2019 (COVID-19) infection typically manifested with mild symptoms, consistent with prior studies.
- No significant differences were noted in diabetes subtype, demographic factors, HbA1c or vaccination status between those with and without COVID-19.
- Unvaccinated children with diabetes who experienced COVID-19 presented with more frequent and higher fevers than vaccinated children.

## Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 was first reported in Wuhan, China, in December 2019, and rapidly spread worldwide.<sup>1)</sup> During the early stages of the

pandemic, the rate of SARS-CoV-2 infection was lower in children, and manifestations of COVID-19 were asymptomatic or less severe compared to those in adults. However, some children experienced a severe clinical course, and a high prevalence of severe COVID-19 was noted in children with comorbidities.<sup>2-5)</sup>

Although pre-existing diabetes does not increase the risk of SARS-CoV-2 infection, it may worsen the outcomes of the disease.<sup>6)</sup> Adults with diabetes have an elevated risk of complications and death from COVID-19.<sup>7,8)</sup> However, unlike adults, children with pre-existing diabetes mellitus (DM)—either type 1, type 2, or monogenic—did not appear to have a higher risk of severe COVID-19 compared to their unaffected peers.<sup>9-11)</sup> This may be due to limited availability of pediatric data, higher prevalence of type 1 diabetes (T1D) versus type 2 diabetes (T2D) in children vs. adults, or higher prevalence of associated comorbidities (e.g., obesity) in adults. Obesity in children with DM might increase the risk of complications due to COVID-19.<sup>12)</sup>

More than 4 years have elapsed since March 11, 2020, when COVID-19 was declared a pandemic. Numerous variants of SARS-CoV-2 have been discovered, and the transmissibility and severity of the virus have gradually changed. Alpha, Beta, and Gamma variants have spread throughout various communities in Korea; however, their detection rate is no more than 50%. The Delta and Omicron variants have caused large-scale community outbreaks in Korea.<sup>13)</sup>

The clinical pediatric COVID-19 data available are currently limited to children with diabetes. Therefore, we investigated the clinical features and outcomes of COVID-19 in children and adolescents with diabetes in Daegu between January and March 2022.

## Materials and methods

### 1. Study population

A total of 123 children and adolescents (59 males and 64 females) with DM and who were younger than 18 years of age were included in this study between January and March 2022. Data were collected from 7 medical centers in Daegu (Daegu Catholic University Hospital, Kyungpook National University Hospital, Kyungpook National University Chilgok Hospital, Keimyung University Dongsan Medical Center [Dongsan Hospital, Daegu Dongsan Hospital], Yeungnam University Hospital, and Daegu Fatima Hospital). DM diagnosis was based on the following criteria obtained from the American Diabetes Association: (1) a random plasma glucose level  $\geq 200$  mg/dL with typical diabetic symptoms, (2) fasting plasma glucose level  $\geq 126$  mg/dL, (3) plasma glucose level  $\geq 200$  mg/dL for 2 hours during an oral glucose (75 g) tolerance test, or (4) glycosylated hemoglobin (HbA1c) level  $\geq 6.5\%$ . The diagnostic criteria for T1D were (1) insulin treatment with decreased C-peptide levels and/or (2) positive autoantibodies. The diagnostic criteria for T2D were (1) symptoms and signs of insulin resistance (acanthosis nigricans, obesity), (2) normal or increased level

of C-peptide, (3) family history of T2D, and (4) use of oral hypoglycemic agents.<sup>14)</sup>

### 2. Methods

From January to March 2022, COVID-19-related data were obtained from a retrospective review of the medical records of patients who received regular in-hospital diabetes care. Clinical characteristics included age, sex, height, weight, body mass index (BMI), BMI standard deviation score (SDS), HbA1c level, comorbidities, medication, and COVID-19 vaccination status. The BMI, determined using sex- and age-specific percentiles from the Korean National Growth Charts, was categorized as normal (BMI < 85th percentile), overweight (BMI  $\geq 85$ th percentile and < 95th percentile), or obese (BMI  $\geq 95$ th percentile).<sup>15)</sup>

Children who tested positive after a reverse transcription polymerase chain reaction assay or rapid antigen test, using nasal or pharyngeal swab specimens, were diagnosed with COVID-19, irrespective of the clinical signs and symptoms present. Clinical data on clinical characteristics; symptom duration during acute illness; physical or mental health symptoms; and persistent, recurrent, or novel complications occurring  $\geq 4$  weeks after COVID-19 infection were collected for all children. We regarded COVID-19 cases as "mild" (upper respiratory tract involvement only) or "moderate" (lower respiratory tract involvement present) if there was no supplemental oxygen requirement.<sup>12)</sup> Those with such a need were categorized as "severe."

### 3. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). Continuous variables were described as medians with interquartile ranges (IQR), and categorical variables were presented as numbers and percentages. The Mann-Whitney test was used to compare 2 groups, and the chi-square test was used to compare proportions. Results were considered statistically significant if  $P < 0.05$ .

### 4. Ethical statement

This study protocol was reviewed and approved by the Institutional Review Board (IRB) of Daegu Catholic University (IRB approval No. CR-22-118). The requirement for informed consent was waived by the IRB.

## Results

### 1. Clinical characteristics of 123 children with diabetes

A total of 123 children and adolescents (73 with T1D and 50 with T2D) was enrolled in the study; those with monogenic DM were excluded (Table 1). This study included 59 males and

64 females. The median age of the patients was 14.6 years (IQR, 12.0–15.9 years). Two patients were 0–5 years of age, 15 patients aged 5–10 years, 57 patients aged 10–15 years, and 49 patients aged 15–18 years. The proportion of patients aged 0–10 years was higher in the T1D group than in the T2D group. Median BMI SDS was 1.3 (IQR, 0.1–2.3), and median HbA1c level was 7.3% (IQR, 6.2%–9.0%). Children with T1D were treated with insulin, while those with T2D were treated with metformin and/or insulin. Fifty-one of the 73 children with T1D (69.9%) used continuous glucose monitoring systems. COVID-19 vaccinations had been received in 68 children. Thirty-five children were diagnosed with COVID-19 (18 patients with T1D, 17 patients with T2D). No significant difference was observed in the number of children diagnosed with COVID-19 between the T1D and T2D groups ( $P=0.177$ ).

### 2. Clinical characteristics of 123 diabetic children according to COVID-19 status

Thirty-five patients were diagnosed with COVID-19. Most of them were over the age of 10. Eighteen of the 35 children diagnosed with COVID-19 and 50 of the 88 children who were not were vaccinated. There were no significant differences in type of DM, sex, age, BMI, HbA1c level, or vaccination status between children with or without COVID-19 (Table 2).

### 3. Clinical characteristics of 35 diabetic children with COVID-19 according to vaccination status

Eighteen of the 35 patients diagnosed with COVID-19 were

vaccinated, and 17 were not. All of the children with DM under the age of 10 were unvaccinated. All children and adolescents with DM had mild symptoms of COVID-19. The most common COVID-19 symptoms reported were fever (65.7%),

**Table 2. Clinical characteristics of 123 diabetes patients according to COVID-19 status**

Variable	COVID-19 (n=35)	Non-COVID-19 (n=88)	P-value
DM type			0.177
T1D	18 (51.4)	55 (62.5)	
T2D	17 (48.6)	33 (37.5)	
Male sex	18 (51.4)	41 (46.6)	0.388
Age (yr)			0.583
<5	1 (2.9)	1 (1.1)	
5, <10	5 (14.3)	10 (11.4)	
10, <15	13 (37.1)	44 (50.0)	
≥15	16 (45.7)	33 (37.5)	
BMI status			0.214
Normal	14 (40.0)	45 (51.1)	
Overweight	4 (11.4)	15 (17.0)	
Obese	17 (48.6)	28 (31.8)	
HbA1c (%)			0.488
<7	17 (48.6)	37 (42.0)	
7, <8.5	8 (22.8)	21 (23.9)	
≥8.5	10 (28.6)	30 (34.1)	
Vaccination, (+)	18 (51.4)	50 (56.8)	0.366

Values are presented as number (%).

COVID-19, coronavirus disease 2019; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycated hemoglobin.

**Table 1. Clinical characteristics of 123 patients with diabetes**

Characteristic	Total (N=123)	T1D (N=73)	T2D (N=50)	P-value
Male sex	59 (48.0)	35 (47.9)	24 (48.0)	0.570
Age (yr)	14.6 (12–15.9)	13.3 (10.4–15.6)	15.2 (14.5–16.5)	<0.001
<5	2 (1.6)	2 (2.7)	0 (0.0)	
5, <10	15 (12.2)	14 (19.2)	1 (2.0)	
10, <15	57 (46.3)	34 (46.6)	23 (46.0)	
≥15	49 (39.8)	23 (31.5)	26 (52.0)	
BMI SDS	1.3 (0.1–2.3)	0.5 (-0.6 to 1.2)	2.5 (1.6–3.3)	<0.001
HbA1c (%)	7.3 (6.2–9.0)	7.0 (6.3–8.9)	7.9 (5.9–9.0)	0.851
Medication				
Insulin, total daily dose (U)/kg	73 (59.3)	73 (100) 0.9 (0.8–1.15)	0 (0)	
Metformin	36 (29.3)	0 (0)	36 (72.0)	
Metformin with insulin, total daily dose (U)/kg	14 (11.4)	0 (0)	14 (28.0) 0.44 (0.37–0.51)	
CGM	53 (43.1)	51 (69.9)	2 (4.0)	<0.001
Vaccinated cases	68 (55.3)	30 (41.1)	38 (76.0)	<0.001
1 Time	3 (2.4)	1 (1.4)	2 (4.0)	
2 Times	46 (37.4)	19 (26.0)	27 (54.0)	
3 Times	19 (15.4)	10 (13.7)	9 (18.0)	
COVID-19 cases	35 (28.5)	18 (24.7)	17 (34.0)	0.177

Values are presented as number (%) or median (interquartile range).

T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; BMI, body mass index; SDS, standard deviation score; HbA1c, glycated hemoglobin; CGM, continuous glucose monitoring; COVID-19, coronavirus disease 2019.

cough (65.7%), and sore throat (60%). Fourteen children presented with a fever of 38°C or higher, lasting for more than 2 days. Eleven of these 14 children were unvaccinated ( $P=0.005$ ). No children with COVID-19 required hospitalization: all were managed safely within their homes. None had post-COVID-19 conditions (Table 3).

#### 4. Factors influencing the 14 COVID-19 diabetic children presenting with a fever of 38°C or higher, lasting for more than 2 days

Among the 14 COVID-19 diabetic children with a fever of 38°C or higher, lasting for more than 2 days, 11 were unvaccinated ( $P=0.004$ ). Among these 11 children, one was <5 years of age, 4 were 5–10 years of age, 5 were 10–15 years of age, and 4 were ≥15 years of age. Eight patients had a BMI less than 85%, and 8 patients had an HbA1c less than 7%. No significant differences were observed in terms of type of DM, sex, age, BMI, and HbA1c levels between patients with COVID-19 who did or did not experience fevers of 38°C or higher. However, a

significant difference in vaccination status was observed (Table 4).

## Discussion

Although fatal outcomes of COVID-19 are rare in children, children with comorbidities are at a higher risk of severe disease.<sup>4)</sup> In Korea, Lee et al.<sup>2)</sup> reported that 8 children, 3 of whom had underlying diseases, experienced critical COVID-19 between January 20, 2020, and October 7, 2021. One who had intellectual disability was newly diagnosed with T2DM alongside COVID-19. Among these 8 children, 7 were obese and one was overweight. Choi et al.<sup>3)</sup> reported 53 children who experienced moderate to critical COVID-19 between January and December 2021. Of these, 3 had diabetes, and 31 were obese. Shin et al.<sup>5)</sup> reported that the case fatality rate decreased from 3.05 per 100,000 in the ≤18-year-old population during the Delta-dominant period (July 25, 2021–January 15, 2022) to 0.82 per 100,000 during the Omicron-dominant period (January 16, 2022–September 3, 2022). There were 46 COVID-

**Table 3. Clinical characteristics of 35 diabetic patients with COVID-19 according to vaccination status**

Characteristic	Total (n=35)	Vac+* (n=18)	Vac-† (n=17)	P-value
DM type				0.127
T1D	18 (51.4)	7 (38.9)	11 (64.7)	
T2D	17 (48.6)	11(61.1)	6 (35.3)	
Male sex	18 (51.4)	12 (66.7)	6 (35.3)	0.063
Age (yr)				0.005
<5	1 (2.9)	0 (0)	1 (5.9)	
5, <10	5 (14.3)	0 (0)	5 (29.4)	
10, <15	13 (37.1)	5 (27.8)	8 (47.0)	
≥15	16 (45.7)	13 (72.2)	3 (17.6)	
BMI SDS	1.6 (0.5–2.6)	1.8 (0.8–2.6)	0.7 (-0.02 to 2.5)	0.075
BMI status				
Normal	14 (40.0)	5 (27.8)	9 (53.0)	
Overweight	4 (11.4)	4 (22.2)	0 (0.0)	
Obese	17 (48.6)	9 (50.0)	8 (47.0)	
HbA1c	7.0 (6.2–8.6)	8.2 (6.2–9.4)	6.8 (6.4–7.7)	
HbA1c (%)				0.012
<7	17 (48.6)	7 (38.9)	10 (58.8)	
7, <8.5	8 (22.8)	2 (11.1)	6 (35.3)	
≥8.5	10 (28.6)	9 (50.0)	1 (5.9)	
Fever	23 (65.7)	9 (50.0)	14 (82.4)	0.047
Fever ≥38°C & ≥2 days	14 (40.0)	3 (16.7)	11 (64.7)	0.005
Cough	23 (65.7)	11(61.1)	12 (70.6)	0.407
Sore throat	21 (60.0)	11(61.1)	10 (58.8)	0.582
Rhinorrhea	10 (28.6)	6 (33.3)	4 (23.5)	0.396
Nasal stuffiness	5 (14.3)	3 (16.7)	2 (11.8)	0.528
Headache	7 (20.0)	4 (22.2)	3 (17.6)	0.534
Myalgia	7 (20.0)	4 (22.2)	3 (17.6)	0.534

Values are presented as number (%) or median (interquartile range).

COVID-19, coronavirus disease 2019; Vac+, vaccinated; Vac-, not vaccinated; DM, diabetes mellitus; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; BMI, body mass index; SDS, standard deviation score; HbA1c, glycated hemoglobin.

\*Eighteen of the 35 patients diagnosed with COVID-19 were vaccinated. †Seventeen of the 35 patients diagnosed with COVID-19 were not vaccinated.



**Table 4. Factors influencing the 14 patients presenting with a fever of 38°C or higher lasting for more than 2 days of the 35 diabetic patients with COVID-19**

Variable	Fever: 38°C or higher (n=14)	Fever: mild or absent (n=21)	P-value
DM type			0.053
T1D	10	8	
T2D	4	13	
Sex			0.129
Male	5	13	
Female	9	8	
Age (yr)			0.096
<5	1	0	
5, <10	4	1	
10, <15	5	8	
≥15	4	12	
BMI status			0.149
Normal	8	6	
Overweight	2	2	
Obese	4	13	
HbA1c (%)			0.674
<7	8	9	
7, <8.5	3	5	
≥8.5	3	7	
Vaccinated cases			0.004
0	11	6	
≥1	3	15	

Values are presented as number of patients.

COVID-19, coronavirus disease 2019; DM, diabetes mellitus; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycosylated hemoglobin.

19-associated deaths in pediatric patients (none in 2020, 3 in 2021, and 43 in 2022) in Korea from the beginning of the pandemic until September 3, 2022. Significant increases in COVID-19 case numbers led to the higher number of deaths in 2022. Of the 46 deaths, 47.8% occurred in patients with underlying diseases, with neurologic disease and malignancies being the most common. DM was present in 1 case. Only 4 cases were vaccinated, while the other 42 cases (91.3%) were not. The importance of vaccination for preventing mortality in children, especially in those with underlying diseases, was emphasized. In Korea, COVID-19 vaccination is recommended for all adolescents (12–18 years), and a booster is highly recommended for high-risk groups. COVID-19 vaccination is optional for all children (5–11 years) but highly recommended for high-risk groups.<sup>16)</sup>

SARS-CoV-2 has evolved over time. In Korea, the overall severity of COVID-19 decreased over the Delta-dominant period and continued to decrease over the Omicron-dominant period.<sup>13)</sup> The rates of intensive care unit admission and mechanical ventilation usage were lower in children and adolescents infected with the Omicron variant as opposed to the Delta variant. Additionally, those aged 6–18 years appeared to have less severe symptoms than those <6 years old.<sup>17)</sup>

Since the first confirmed COVID-19 case on 20 January 2020

(entry from Wuhan, China), Korea designated and managed COVID-19 as a class 1 infectious disease in accordance with the Infectious Disease Control and Prevention Act. On 25 April 2022, COVID-19 was reclassified as a class 2 infectious disease based on the reduced severity of the outbreak, advanced response strategies, high vaccination rate, availability of oral therapeutics, and the features of the prevalent Omicron variant.<sup>18)</sup>

This study showed that, in all children and adolescents with pre-existing diabetes, COVID-19 infection was associated with mild symptoms from January to March 2022. These findings are consistent with those of previous studies.<sup>9-11)</sup> No significant differences were observed between patients with or without COVID-19 in terms of type of DM, sex, age, BMI, HbA1c level, or vaccination status. High HbA1c level does not appear to increase the risk of SARS-CoV-2 infection. COVID-19 increases the risk of glycemic imbalances,<sup>9)</sup> and obesity may cause severe COVID-19 in children with DM.<sup>12)</sup> However, in the present study, high BMI or HbA1c level did not appear to worsen the COVID-19-related outcomes, although unvaccinated children with COVID-19 presented with more frequent higher fever than did vaccinated children. During this study period, patients with COVID-19 quarantined themselves at home. Some patients with hyperglycemia were given advice telephonically to avoid the need for urgent care in an emergency department. More than half of the patients with T1D used continuous glucose monitoring (CGM), which improves glycemic balance and reduces the risk of hypoglycemia. All the patients in this study were safely managed in their homes. Children with DM require uninterrupted access to medical care and should be strictly monitored by parents and pediatricians.<sup>10)</sup> Telemedicine and online consultations allow patients to remain in close contact without person-to-person contact, minimizing the risk of infection and metabolic decompensation. In addition, concerns regarding COVID-19 should not prevent appropriate referrals for the required care.

Although there were T1D patients with deterioration of glycemic value due to decreased physical activity, increased consumption of carbohydrates, and mood deterioration,<sup>19)</sup> the pandemic lockdown has not led to a significant decline in glycemic control in children with pre-existing T1D. This is likely due to their parents remaining at home and providing strict monitoring of blood glucose levels, which may be associated with improved self-care, regular daily lifestyle, and digital diabetes management.<sup>20)</sup> In contrast, lockdown resulted in short-term worsening of the glycemic values in children and adolescents with pre-existing T2D.<sup>20)</sup> During the pandemic, low physical activity and inappropriate diet indirectly caused increase in body weight and BMI<sup>21-23)</sup> and in the incidence of T2D.<sup>24,25)</sup> In addition, increased frequency and severity of diabetic ketoacidosis (DKA) at the time of DM diagnosis was reported in several studies.<sup>26-29)</sup> This increase in DKA at the time of diagnosis was the result of delays in diagnosis due to difficulties in accessing healthcare and lack of parental recognition of the common symptoms of diabetes.<sup>26-29)</sup>

A study by the Centers for Disease Control found that

children diagnosed with COVID-19 are at higher risk of developing T1D or T2D after infection.<sup>30)</sup> SARS-CoV-2 may lead to diabetes through direct attack of pancreatic  $\beta$  cells and, indirectly, through a cytokine storm. After SARS-CoV-2 infection, the risk of a new diagnosis of diabetes increased in both children and adults.<sup>30,31)</sup> Therefore, clinicians should consider new-onset diabetes as a possible consequence of the metabolic imbalance caused by SARS-CoV-2 infection.<sup>32)</sup>

Our study has several limitations. Since the data were from 7 medical centers in Daegu, the study participants, owing to their geographic location, may not be representative of the general population of Korea. Therefore, a large-scale study involving a national population is required. Other limitations include potential biases introduced by the patients' memory regarding information related to COVID-19. This information was obtained during regular in-hospital check-ups for diabetes care, and detailed clinical findings were not available. In addition, the HbA1c tests were not performed at diagnosis of COVID-19. Therefore, the HbA1c levels were analyzed using the test performed closest in time to COVID-19 diagnosis.

In conclusion, owing to the decreased COVID-19 disease severity, high vaccination rates, uninterrupted access to medical care, and CGM, all children and adolescent diabetic patients with COVID-19 assessed in Daegu between January and March 2022, had mild symptoms of COVID-19. However, unvaccinated children with COVID-19 presented with more frequent higher fevers than did vaccinated children. Although the outcomes related to COVID-19 appeared similar among children with or without DM, children with DM are at increased risk of glycemic imbalance.<sup>9,10)</sup> Therefore, we recommend that clinicians take all possible measures to tighten glycemic control, administer vaccinations, and detect critical cases of COVID-19 early in such children. Further research is required to evaluate the long-term effects of COVID-19 on children and adolescents with DM.

## Notes

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**Author contribution:** Conceptualization: JKK, NWL, YMK, SJK, KMJ, HSK, JEM; Data curation: JKK, NWL, YMK, SJK, KMJ, HSK, JEM; Formal analysis: JKK, NWL; Methodology: JKK, NWL, YMK, YHK, SJK, KMJ, HSK, JEM; Project administration: JKK, YMK, YHK; Visualization: JKK, NWL; Writing - original draft: JKK, NWL, YMK; Writing - review & editing: NWL

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