

Article type: Narrative mini-review

COVID-19: Considerations for Children and Adolescents with Diabetes

Authors, their degrees, designations, and affiliations

1. **Devi Dayal**, MD, Professor, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh.
2. **Arti Yadav**, DM, Registrar, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh.

Correspondence

Dr Devi Dayal

Endocrinology and Diabetes Unit, Department of Pediatrics, 3108, Level III, Advanced Pediatrics Center, Postgraduate Institute of Medical Education and Research, Chandigarh-160012, India.

Tel: +91-172-2755657 (O) +91-172-2772777 (R) +919872072472 (M)

Fax: 0091-172-2744401; 2745078

E-mail: drdevidayal@gmail.com; dayal.devi@pgimer.edu.in

Sources of funding: None

Conflict of interest: None

Statement of ethics: All relevant ethical guidelines were followed for conducting the review and presenting the data.

Abstract

Recent reports suggest that the clinical course of coronavirus disease 2019 (COVID-19) in previously healthy children is usually milder as compared to adults. However, children with comorbid conditions such as diabetes are at increased risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well as morbidity and mortality due to COVID-19. Experience in adults with diabetes shows that they are prone to faster metabolic decompensation, develop diabetes-related complications, and have a poor prognosis when hospitalized with COVID-19. Data on children are limited. The aim of this mini-review is to discuss the possible risks to children and adolescents with diabetes during the current pandemic and the special considerations in management in those affected with COVID-19. The challenges for children who develop new-onset type 1 diabetes during the COVID-19 lockdown, especially in accessing healthcare, are also discussed.

Keywords: Coronavirus disease 2019, COVID-19, children, diabetes, type 1 diabetes, type 2 diabetes, recommendations

Background

The ongoing pandemic of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in unprecedented devastation during modern times. Although the overall experience of the COVID-19 in children suggests that the disease takes a milder course, there is also a concern about its progression to critical disease and death in children with comorbidities, similar to the experience in adult patients (1, 2). In the pediatric population, the impact of COVID-19 appears strikingly similar to the 2009 pandemic caused by the H1N1 virus considered structurally similar to SARS-CoV-2. An Italian study reported that all 13% of children with H1N1 infection who required intensive care had comorbidities indicating a higher risk of severe disease in children with comorbidities (3). At present, it is not fully known whether diabetes increases susceptibility to COVID-19, but there is a general perception of a higher risk of infection and severe disease in people with diabetes. Diabetes is the most common endocrine condition in children, and children with diabetes, whether type 1 (T1D) or type 2 (T2D), who acquire COVID-19, need special consideration during management.

What is the risk?

There are two types of risks connected with COVID-19 in children with diabetes. The first is the risk of acquiring infection and the second is the risk of progression to critical disease or death. Although the data are scarce, children with well-controlled diabetes (average HbA1c level $\leq 7.5\%$) do not appear to be at increased risk for getting infected with SARS-CoV-2 or progress to severe disease (4). Experience during previous epidemics and pandemics is also reassuring (5). In a Spanish study that reported data on diabetes patients hospitalized with influenza during the 2009 pandemic, none of the 37 children and adolescents died as compared to the case fatality rate of about 3% among adults with diabetes (5). During the same pandemic, an Italian study also reported no mortality despite a high risk of severe disease in children with comorbid conditions (3).

Who are at risk?

The risk of susceptibility to SARS-CoV-2 and progression to severe COVID-19 appears to be increased in the following groups of children with diabetes:

Poor metabolic control

Children with poorly controlled diabetes have increased susceptibility to bacterial and fungal infections due to various alterations in their immune response, such as decreased T-lymphocyte and neutrophil function, decreased inflammatory cytokine secretion, decreased complement system and anti-oxidant system responses, and probably decreased antibody response (6, 7). The risk of getting infected with SARS-CoV-2 also increases in patients with poor control of diabetes (6). Consequently, the risk of diabetes-related complications such as diabetic ketoacidosis (DKA) as well as progression to severe COVID-19 increases in these patients. Recent reports suggest that the risk of progression to severe COVID-19 is increased in adult patients with poorly controlled diabetes due to several factors, such as the release of tissue injury-related enzymes, excessive uncontrolled inflammation responses, hypercoagulability, and dysregulation of glucose metabolism (8). There is no substantial reason to believe that the clinical course of children with poorly controlled diabetes and COVID-19 could be different from what has been observed in adult patients. A particular reason for worry is that poor

glycemic control is fairly common in pediatric diabetes populations across the globe; less than 50% only are able to achieve the desired HbA1c targets even in the most developed countries (9, 10). In addition to poor long-term metabolic control, glycemic variability was identified as a significant risk factor for progression to severe disease during previous influenza epidemics (11).

Diabetes with obesity

Recent data indicate that in patients with COVID-19, obesity is a significant risk factor for admission to acute and critical care (12). COVID-19 patients with a body mass index (BMI) of ≥ 30 were almost twice as likely to require hospitalization in the emergency room or intensive care (12). Children with diabetes and obesity are thus particularly vulnerable groups at risk for severe COVID-19. In developed countries, obesity is common in children and adolescents with diabetes (13). The COVID-19 pandemic has further created obesogenic environments for children, particularly those living in urban areas due to several factors such as lack of physical activities resulting from social distancing measures and indoor stay, increased out-of-school time, consumption of high-calorie foods, and increased screen time (14). The resultant increase in their BMI during this pandemic may further increase the risk for COVID-19 complications in obese children with diabetes.

Other co-morbid conditions

Several children and adolescents with diabetes may have associated comorbidities such as cardiovascular disease, mental disorders, epilepsy, pulmonary disease, celiac disease, and other autoimmune disorders (15). There is a lack of data in children, but adults with such comorbid conditions are observed to be an increased risk of morbidity and mortality due to COVID-19 (8, 16). In particular, a worsening of psychosocial problems, quite prevalent in children with diabetes, may occur during stressful pandemic times and lead to a deterioration of glycemic control (17, 18). Furthermore, the two important support groups of children with diabetes i.e. parents and treating physicians, may themselves be under significant pandemic stress and may show an inability to appropriately respond to the needs of these children (18).

Risk due to medications

For pathogenic effects, human coronaviruses including SARS-CoV-2, bind to target cells via angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels (19). Patients with diabetes on treatment with ACE inhibitors and angiotensin II type-1 receptor blockers show increased expression of ACE2, which may facilitate infection with SARS-CoV-2 (19). Similarly, thiazolidinediones and ibuprofen may also increase ACE2 expression. However, further research is needed to establish the role of these drugs, commonly used in patients with diabetes with or without hypertension, in acquisition of SARS-CoV-2 infection or progression to severe COVID-19 (19).

Infants with diabetes

Recent data suggest that infants are more likely to progress to severe COVID-19 (1, 2). The inability to control their food intake during the infection episode may also contribute to a rapid deterioration in metabolic control in infants with diabetes.

Non-availability of insulin

Disruption in the supply chain of drugs, including insulin, during the pandemic may have adverse consequences for children with diabetes, particularly those living in less developed countries.

Concomitant vitamin D deficiency

Vitamin D deficiency (VDD) in children with T1D is associated with poor glycemic control (20), which is a recognized risk factor for susceptibility to various types of infections, including viruses (6, 8, 11). Conversely, vitamin D sufficiency improves metabolic control in children with diabetes (21). A recent review indicated that VDD probably played a role in the initiation and spread of the COVID-19 pandemic and that vitamin D supplementation may not only reduce the risk of infection but also the mortality associated with COVID-19 (22). The risk of VDD increases with staying indoors, which is enforced during lockdown (23). And there is a further risk of exacerbation of VDD in patients requiring hospitalization (24). It is therefore important that children with diabetes remain vitamin D sufficient during the ongoing pandemic.

Recommendations for children with previously diagnosed diabetes

Several professional organizations have issued guidelines for children with diabetes based on experts' views (4). These advisories to parents and caregivers emphasize the importance of remaining vigilant by strict application of measures to prevent COVID-19 infection in children with diabetes (4, 25).

Preventive measures

General preventive measures include maintaining social distancing, thorough and frequent hand washing with soap and water or using alcohol-based rubs, observing respiratory hygiene i.e. covering the mouth and nose with bent elbow while coughing or sneezing, avoiding touching of the mouth, nose, and eyes, using recommended face masks, avoiding non-essential travel, and adhering to a nutritional plan particularly avoiding calorie dense foods.

Regular physical exercise improves glycemic control and boosts immunity (25). In view of outdoor restrictions, children and adolescents with diabetes may be advised doing simple exercises such as rope skipping, and walking, jogging, or running in the lawns.

Although casual sunexposure for about 30 minutes per day may prevent VDD, the efficacy of sunexposure to raise serum vitamin D to optimal levels cannot be relied upon during critical pandemic times (26). A rapid increase in serum vitamin D levels is desirable. Adolescents with body weight similar to adults are recommended to consider taking 10,000 IU per day of cholecalciferol for a few weeks followed by 5000 IU per day (22). Alternatively, a weekly dose of 60,000 IU for 4 weeks followed by a lower daily dose may be advised. For younger children, half of the adult doses may suffice; the goal should be to raise serum vitamin D concentrations to 40-60 ng/mL (100-150 nmol/L) (22). Higher doses may be useful for patients who require hospitalization for COVID-19 (22).

Measures after infection with SARS-CoV-2

The glycemic control may deteriorate after infection with SARS-CoV-2. For those not requiring hospitalization, strict adherence to the sick day management guidelines is recommended (4, 25). In general, the guidelines include:

1. More frequent monitoring of blood glucose and urine or blood ketone with the aim to keep blood glucose levels at 70-180 mg/dL (4-10 mmol/L) and blood ketone levels below 0.6 mmol/L. Insulin should not be stopped; the treating doctors must advise parents to have back up insulins (without stockpiling) in countries where there may be disruption in the insulin supply chain during the pandemic.
2. Children with T2D on oral hypoglycemic drugs may need to modify their drug doses and initiate insulin in consultation with their treating specialist. In particular, certain medications that cause volume depletion, such as Dapagliflozin, need to be avoided.
3. Parents should keep a watch for dehydration and treat symptoms such as fever.
4. In the following circumstances, specialist advice for possible hospital referral needs to be obtained:
 - a. Persistence of fever or vomiting suggests worsening dehydration and potential circulatory compromise.
 - b. Persistent elevation of blood ketones (>1.5 mmol/L) or urine ketones (large) despite the use of correctional doses of insulin and/or fruity breath odor, which indicates DKA.
 - c. Presence of signs of exhaustion, confusion, abdominal pain, or fast breathing.

In hospital management

About half of the non-diabetic patients with COVID-19 experience hyperglycemia predominantly due to endogenous stress-induced glucocorticoid hypersecretion (27). Experience during previous epidemics suggests that viruses structurally similar to SARS-CoV-2 may cause transient impairment of pancreatic islet cell function or modulate the action of insulin via anchoring to host cells via dipeptidyl peptidase 4 (27). Thus, the possibility that blood glucose control may worsen during hospitalization with COVID-19 is high. Based on the recent experience of poor prognosis in diabetic adults hospitalized with COVID-19, good inpatient glycemic control is particularly important in the comprehensive management of these patients (8, 16, 25). Children on oral anti-diabetic drugs may preferably shift to subcutaneous insulin during hospitalization with COVID-19. In those with T1D, insulin therapy may need intensification. However, blood glucose targets and treatment strategies need to be individualized. The aim is to avoid both hyperglycemia and hypoglycemia or glycemic variability, which is associated with a poorer prognosis in hospitalized patients (11, 16).

Blood sugar targets in children hospitalized with mild COVID-19 are slightly more stringent than in non-sick states i.e. fasting plasma glucose 80-110 mg/dL (4.4-6.1. mmol/L) and 2-hour postprandial plasma glucose of 110-140 mg/dL (6.1-7.8. mmol/L). A seven-point or more frequent blood sugar monitoring and continuation of the previous insulin regimen with frequent correctional boluses are recommended (16, 25).

All diabetic children with severe or critical COVID-19 and/or any complications of diabetes require management in an intensive care unit. These children are at risk of developing DKA or hyperglycemic hyperosmolar status because of the rapid changes in their condition and require insulin infusion therapy. The blood glucose targets are relatively less stringent in order to avoid glycemic variability; the usual target non-fasting blood glucose range is 140-180 mg/dL (7.8-10.0. mmol/L).

Recommendations for new-onset T1D

Children with new-onset T1D during the COVID-19 pandemic are at risk of deterioration to DKA due to several factors, such as the inability to take timely medical advice due to either fear of becoming infected with SARS-CoV-2 in hospital settings or closure of non-COVID

care due to redistribution of healthcare resources, and difficulties in healthcare access due to severe lockdown restrictions (28, 29). In regions where hospitals are overburdened with COVID-19 care, children with new-onset T1D without DKA can be easily managed without hospitalization with prompt initiation of insulin. Even non-severe DKA may respond well to closely supervised initiation of subcutaneous rapid-acting insulin either in the emergency room or outpatient department, thus avoiding admission into the intensive care unit besieged by COVID-19 (30). This is especially important for countries with poor healthcare infrastructure and are under severe resource crunch during the COVID-19 pandemic.

Conclusions

Children and adolescents with previously diagnosed or new-onset diabetes need special considerations for management during the COVID-19 pandemic. Strict blood sugar control may help them escape infection with SARS-CoV-2 as well as morbidity and mortality due to COVID-19. Parents and treating physicians need to be extra vigilant to help these children through the pandemic crisis. The government and professional bodies should run aggressive media campaigns to make parents fully aware that they should not ignore initial symptoms of new-onset T1D in their children and seek timely medical attention even during the COVID-19 lockdown.

References

1. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr.* 2020;109(6):1088-1095.
2. Dayal D. We urgently need guidelines for managing COVID-19 in children with comorbidities. *Acta Paediatr.* 2020 Apr 12. doi: 10.1111/apa.15304. [Epub ahead of print]
3. Nenna R, Papoff P, Moretti C *et al.* Detection of respiratory viruses in the 2009 winter season in Rome: 2009 influenza A (H1N1) complications in children and concomitant type 1 diabetes onset. *Int J Immunopathol Pharmacol* 2011; 24:651–659.
4. ISPAD position statement on COVID-19 and Children with Diabetes, March 19, 2020. Available at: <https://www.ispad.org/news/COVID-19>. Accessed on April 10, 2020.
5. Jiménez-García R, Hernández-Barrera V, Rodríguez-Rieiro C, Lopez de Andres A, de Miguel-Diez J, Jimenez-Trujillo I, et al. Hospitalizations from pandemic Influenza [A(H1N1)pdm09] infections among type 1 and 2 diabetes patients in Spain. *Influenza Other Respir Viruses.* 2013;7(3):439-47.
6. Calliari LE, Almeida FJ, Noronha RM. Infections in children with diabetes. *J Pediatr (Rio J).* 2020;96 Suppl 1:39-46.
7. Dayal D, Jain P, Kumar R, Bakshi J, Menon P, Das A, Singhi S, Singh M. Clinical spectrum and outcome of invasive filamentous fungal infections in children with Type 1 diabetes: North Indian experience. *Clin Pediatr Endocrinol.* 2015;24(2):51-7.
8. Kosinski C, Zanchi A, Wojtuszczyzn A. Diabète et infection à COVID-19 [Diabetes and COVID-19 infection]. *Rev Med Suisse.* 2020;16(692):939-943.
9. Ogle GD, von Oettingen JE, Middlehurst AC, Hanas R, Orchard TJ. Levels of type 1 diabetes care in children and adolescents for countries at varying resource levels. *Pediatr Diabetes.* 2019;20(1):93-98.

10. Charalampopoulos D, Hermann JM, Svensson J, Skriverhaug T, Maahs DM, Akesson K, et al. Exploring Variation in Glycemic Control Across and Within Eight High-Income Countries: A Cross-sectional Analysis of 64,666 Children and Adolescents With Type 1 Diabetes. *Diabetes Care*. 2018;41(6):1180-1187.
11. Hulme KD, Gallo LA, Short KR. Influenza Virus and Glycemic Variability in Diabetes: A Killer Combination? *Front Microbiol*. 2017;8:861.
12. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, Stachel A. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. *Clin Infect Dis*. 2020 Apr 9. pii: ciaa415. doi: 10.1093/cid/ciaa415. [Epub ahead of print]
13. Buzzetti R, Zampetti S, Pozzilli P. Impact of obesity on the increasing incidence of type 1 diabetes. *Diabetes Obes Metab*. 2020 Mar 10. doi: 10.1111/dom.14022. [Epub ahead of print]
14. Rundle AG, Park Y, Herbstman JB, Kinsey EW, Wang YC. COVID-19 Related School Closings and Risk of Weight Gain Among Children. *Obesity (Silver Spring)*. 2020 Mar 30. doi: 10.1002/oby.22813. [Epub ahead of print]
15. Fazeli Farsani S, Souverein PC, van der Vorst MM, Knibbe CA, de Boer A, Mantel-Teeuwisse AK. Chronic comorbidities in children with type 1 diabetes: a population-based cohort study. *Arch Dis Child*. 2015;100(8):763-8.
16. Gentile S, Strollo F, Ceriello A. COVID-19 infection in Italian people with diabetes: Lessons learned for our future (an experience to be used). *Diabetes Res Clin Pract*. 2020;162:108137.
17. Agrawal J, Kumar R, Malhi P, Dayal D. Prevalence of psychosocial morbidity in children with type 1 diabetes mellitus: a survey from Northern India. *J Pediatr Endocrinol Metab*. 2016;29(8):893-9.
18. Ornell F, Schuch JB, Sordi AO, Kessler FHP. "Pandemic fear" and COVID-19: mental health burden and strategies. *Braz J Psychiatry*. 2020 Apr 3. pii: S1516-44462020005008201. [Epub ahead of print]
19. Mali SN, Thorat BR, Chopade AR. A Viewpoint on Angiotensin-Converting Enzyme 2, Anti-Hypertensives and Coronavirus Disease 2019 (COVID-19). *Infect Disord Drug Targets*. 2020 May 10;10.2174/1871526520666200511005546. [Epub ahead of print]
20. Wierzbicka E, Szalecki M, Pludowski P, et al. Vitamin D status, body composition and glycemic control in Polish adolescents with type 1 diabetes. *Minerva Endocrinol* 2016; 41: 445-455.
21. Panjiyar RP, Dayal D, Attri SV, Sachdeva N, Sharma R, Bhalla AK. [Sustained serum 25-hydroxyvitamin D concentrations for one year with cholecalciferol supplementation improves glycaemic control and slows the decline of residual β cell function in children with type 1 diabetes]. *Pediatr Endocrinol Diabetes Metab*. 2018;2018(3):111-117.
22. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*. 2020;12(4). pii: E988.
23. Dayal D, Jayaraman D. Vitamin D deficiency: Dealing with the current epidemic. In: Singhi S, Mathew J, editors. *Current Pediatrics Practice*. 3rd ed. New Delhi: Peepee Publishers; 2015. p. 69-75.
24. Dayal D, Kumar S, Sachdeva N, Kumar R, Singh M, Singhi S. Fall in Vitamin D Levels during Hospitalization in Children. *Int J Pediatr*. 2014;2014:291856.

25. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr.* 2020;14(3):211-212. doi:10.1016/j.dsx.2020.03.002
26. Lee YM, Kim SA, Lee DH. Can Current Recommendations on Sun Exposure Sufficiently Increase Serum Vitamin D Level?: One-Month Randomized Clinical Trial. *J Korean Med Sci.* 2020;35(8):e50.
27. Ilias I, Zabuliene L. Hyperglycemia and the novel Covid-19 infection: Possible pathophysiologic mechanisms. *Med Hypotheses.* 2020;139:109699.
28. Dayal D, Gupta S, Raithatha D, Soni P, Kumar S, Baranwal A. Near-fatal experience due to delayed diagnosis of type 1 diabetes during the COVID-19 pandemic. April 28, 2020, PREPRINT (Version 1). Available at Research Square <https://doi.org/10.21203/rs.3.rs-25337/v1>.
29. Dayal D, Gupta S, Raithatha D, Jayashree M. Missing during COVID-19 lockdown: children with new-onset type 1 diabetes. May 13, 2020, PREPRINT (Version 1). Available at Research Square <https://doi.org/10.21203/rs.3.rs-28594/v1>.
30. Edholm K, Lappé K, Kukhareva P, et al. Reducing Diabetic Ketoacidosis Intensive Care Unit Admissions Through an Electronic Health Record-Driven, Standardized Care Pathway. *J Healthc Qual.* 2020;10.1097/JHQ.0000000000000247.