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COVID-19: Considerations for Children and Adolescents with Diabetes

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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 co-morbid 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 hospitalised with COVID-19. The data in children is 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.

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

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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 an unprecedented devastation during modern times. Although the overall experience of 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 those with comorbidities, similar to the experience in adult patients (1, 2). A striking similarity of COVID-19 pandemic to the 2009 pandemic caused by H1N1 virus considered structurally similar to SARS-CoV-2, is being observed in the pediatric population; all the 13% children with H1N1 infection in an Italian study who required intensive care had co-morbidities indicating a higher risk for severe infection in children with comorbidities (3). At present, it is not fully known if 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 being the most common endocrine condition in children, children with diabetes whether type 1 (T1D) or type 2 (T2D) who acquire COVID-19 need special considerations during management.

What is the risk?

There are two types of risks connected with COVID-19 in children with diabetes. First is the risk of acquiring infection and second the risk of progression to critical disease or death. Although the data is scarce, children with well controlled diabetes (average HbA1c level ≤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 similar to COVID-19 pandemic, is also reassuring (5). In a Spanish study that reported data on diabetes patients hospitalized with influenza during 2009 pandemic, none of the 37 children and adolescents died as compared to case fatality rate of about 3% amongst adult diabetics (5). During the same

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pandemic, an Italian study also reported no mortality despite a high risk of severe disease in children with co-morbid conditions (3).

Who are at risk?

The risk of susceptibility and progression to severe disease appears to be increased in the following groups of children with diabetes:

Poor metabolic control

Children with poorly controlled diabetes have increase susceptibility to bacterial and fungal infection 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 by 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 of adult diabetes patients with COVID-19 suggest an increased risk of severity due to several factors such as 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 the poor long-term metabolic control, glycemic variability was identified as a significant risk factor for severe disease during previous influenza epidemics (11).

Diabetes with obesity

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Recent data indicates that in patients with COVID-19, obesity is a significant risk factor for admission to acute and critical care (12). COVID-19 patients with body mass index (BMI) of ≥30 were almost twice more likely to require hospitalisation in emergency room or intensive care (12). Children with diabetes and obesity are thus a particularly vulnerable group at risk for severe COVID-19. In the developed countries, obesity is common in children and adolescents with diabetes (13, 14). 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, increased screen time etc (15). The resultant increase in their BMI during this pandemic has further increased 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 disorders, mental disorders, epilepsy, pulmonary disease, celiac disease and other autoimmune disorders (16). There is lack of data in children but adults with such co-morbid conditions are observed to be at increased risk of morbidity and mortality due to COVID-19 (8, 17). In particular, a worsening of psychosocial problems, quite prevalent in children with diabetes, may occur during the stressful pandemic times and lead to a deterioration of glycemic control with further implications for COVID-19 severity (18, 19). Furthermore, the two important support groups of children with diabetes i.e. parents and the treating physicians may themselves be under significant pandemic stress and may show inability to appropriately respond to the needs of these children (19).

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,

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intestine, kidney, and blood vessels (20). Patients with diabetes on treatment with ACE inhibitors and angiotensin II type-1 receptor blockers show increased expression of ACE2 that may facilitate infection with SARS-CoV-2 (20). Similarly, thiazolidinediones and ibuprofen also increase ACE2 expression. All these drugs used in patients with diabetes with or without hypertension may thus increase their risk of developing severe COVID-19 (20).

Infants with diabetes

Recent data suggests that infants are more likely to progress to severe COVID-19 and death (1, 2). The inability to control their food intake during infection may also contribute to a fast deterioration in metabolic control.

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 (21), which is a recognised risk factor for predisposition and severity of various types of infections including viruses (6, 8, 11). Conversely, vitamin D sufficiency improves metabolic control in children with diabetes (22). A recent review indicates that VDD probably played a role in the initiation and spread of COVID-19 pandemic and that vitamin D supplementation may not only reduce the risk of infection but also the mortality associated with COVID-19 (23). The risk of VDD increases with staying indoors (24). And there is further risk of exacerbation of VDD in patients requiring hospitalisation (25). It is therefore important that children with diabetes remain vitamin D sufficient during the ongoing pandemic.

Recommendations for children with diabetes

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Several professional organisations have issued guidelines for children with diabetes based on the experts' views (4). These advisories to parents and caregivers emphasize on the importance of remaining vigilant by strict application of measures to prevent COVID-19 infection in children with diabetes (4, 26).

Preventive measures

The 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 mouth and nose with bent elbow while coughing or sneezing, avoiding touching of mouth, nose and eyes, using recommended face masks, avoiding non-essential travel, and adhering to nutritional plan in particular avoiding calorie dense foods.

Regular physical exercise improves glycemic control and boosts immunity (26). In view of outdoor restrictions, children and adolescents with diabetes may be advised doing simple exercises such as rope skipping, walking in the lawns or surroundings for about an hour twice daily, jogging or running etc.

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 the present critical times (27). 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 (23). 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) (23). Higher doses may be useful for those who get infected with COVID-19 and require hospitalization (23).

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Measures after infection with SARS-CoV-2

The glycemic control may deteriorate after infection with SARS-CoV-2. For those not requiring hospitalisation, a strict adherence to the sick day management guidelines is recommended (4, 26). In general, the guidelines include:

1. More frequent monitoring of blood glucose, and urine or blood ketone with an aim to keep blood glucose levels at 70-180 mg/dL (4-10 mmol/L) and blood ketones 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 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 suggesting worsening dehydration and potential circulatory compromise.
    b. Persistent elevation of blood ketones (>1.5 mmol/L) or urine ketones (large) despite use of correctional doses of insulin and/or fruity breath odour that indicates DKA.
    c. Presence of signs of exhaustion, confusion, abdominal pain or fast breathing.

In hospital management

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About half of the non-diabetic patients with COVID-19 experience hyperglycemia due predominantly to endogenous stress-induced glucocorticoid hypersecretion (28). 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 due to anchoring to host cells via dipeptidyl peptidase 4 (28). Thus the possibility that blood glucose control may worsen or during hospitalisation with COVID-19 is high. Based on the recent experience of a poor prognosis in diabetic adults hospitalised with COVID-19, good inpatient glycemic control is particularly important in the comprehensive management of these patients (8, 17, 26). Children on oral anti-diabetic drugs are preferably shifted to insulin during hospitalisation with COVID-19. In those with T1D, the insulin therapy needs intensification. The blood glucose targets and treatment strategies need to be individualized. The aim is to avoid both hyperglycemia and hypoglycemia technically called glycemic variability which is associated with a poorer prognosis in patients with diabetes and COVID-19 (17).

Blood sugar targets in children hospitalised with mild COVID-19 are slightly more stringent as compared to non-sick state i.e. fasting plasma glucose (FPG) 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 (17, 26).

All diabetic children with severe or critical COVID-19 and/or any complication 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. They need to be initiated on insulin infusion therapy. The blood glucose targets are relatively less stringent to avoid glycemic variability; a usual target non-fasting blood glucose range is 140-180 mg/dL (7.8-10.0 mmol/L).

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In conclusion, children and adolescents with diabetes need special considerations for management during the current COVID-19 pandemic. A 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 specialists need to be extra vigilant to help these children through the pandemic crisis.

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