Review Article

COVID-19 and Diabetes in Children: A Narrative Review

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ABSTRACT

Background: COVID-19 is an unknown and novel virus that creates a challenge with all comorbid conditions, including diabetes mellitus (DM). Although DM has not been determined as a definite risk factor for COVID-19 in childhood, clinicians should consider the potential association between DM and COVID-19.

Objectives: This study aimed to review COVID-19 and DM comorbidity in children.

Methods: ISI Web of Science, PubMed, and Google Scholar were investigated to find relevant articles regarding COVID-19 and DM.

Results: Data revealed 50% higher fatal outcomes of COVID-19 in DM children than in healthy ones. Because of the importance of DM in children, it seems mandatory to consider type 1 diabetes and its consequences on COVID-19.

Conclusions: Understanding the pathophysiology of COVID-19 and its interaction with DM are helpful for better management of the disease. These considerations can help clinicians make better decisions about the treatment modalities, management, and diabetic ketoacidosis treatment.

1. Introduction

COVID-19 is a semi-recognized virus that can be a challenge for all comorbid conditions such as diabetes mellitus (DM). Children, like adults, are at risk of COVID-19 infection (1). Type 1 diabetes (T1DM) is one of the major endocrine disorders in childhood (2). Recent study in Iran showed that it occurs in 48 cases per 100000 people (50 and 36 cases per 100000 girls and boys, respectively) (3).

Although limited studies have been conducted on children, it seems that hospitalized children, like adults, have a poor prognosis when infected with COVID-19 (4). Regarding the outbreak of COVID-19 and the importance of its effects on different diseases and based on

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the importance of DM in children, this study aimed to review the different aspects of COVID-19 in DM children.

2. Evidence Acquisition

This research is a narrative review of COVID-19 and DM in children. This review included articles that assessed the association between COVID-19 and DM in children. ISI Web of Science, PubMed, and Google Scholar were investigated to find relevant articles regarding COVID-19 and DM from January 2020 to January 2021. The key terms were "COVID-19," "child," and "Diabetes Mellitus." The authors included all study types assessing the pathophysiology of COVID-19 in DM, mortality rate, the possible mechanism of increasing the risk of COVID-19 in diabetic patients, and the appropriate treatment.

2. Results

Pathophysiology of COVID-19 in DM

COVID-19 has four proteins of spike, membrane, nucleocapsid, and envelope. Spike is one of the most important COVID-19 proteins. It regulates the binding capacity of the host through the receptor binding zone. When these proteins enter the body, they should bind to angiotensin-converting enzyme II (ACE-II) receptors. ACE-II is the receptor of COVID-19 that converts angiotensin II to angiotensin I-VII. Abundant ACE-II immunostaining exists in the upper respiratory system, alveolar cells, heart, endothelial cells, kidneys, enterocytes, pancreas, ileum, and testis. In DM patients, the adherence of the spike protein to the ACE-II receptor and the existence of furin as a cellular protease assist the virus entrance into cells and cause inflammatory responses through the activation of the proinflammatory cytokines and recruitment of inflammatory cells. This process induces apoptosis or necrosis of the infected cells.

Current evidence suggests that COVID-19 can produce cytokine storm resulting from excessive immune reactions and extensive tissue damage. The cytokine storm in DM is activated due to lower T-cell function that relieves the inhibition of the innate immune system. Elevated levels of circulating cytokines have a significant impact on COVID-19 hyperinflammation and lead to multiorgan failure (5, 6). COVID-19 can increase the risk of lymphocytopenia due to the apoptosis of lymphocytes. The degree of lymphocytopenia can indicate the severity of COVID-19. DM can exacerbate the infection through different mechanisms such as blunt anti-viral interferon, decreased complement system, anti-oxidant system responses, decreased antibody response, and humoral immunity (5).

Mortality rate in diabetic children with COVID-19

Although DM is not a definite risk factor for mortality in COVID-19 in childhood, clinicians should consider it. A study reported that the odds of death rate in hospitalized patients with T1DM is 3.5 times higher than that in healthy individuals (7). Another study reported 2.19 as the hazard ratio of the mortality rate of COVID-19 among those with higher HbA1c (>10%) compared to lower levels (6.5%-7%). Furthermore, they mentioned that diabetic ketoacidosis (DKA) was associated with a higher mortality rate. In patients with COVID-19, blood glucose (BG) level and DM are independent predictors of mortality and morbidity (8).

There are important challenges to decreasing the mortality rate in COVID-19 patients. One of them is the effect of administering drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). Based on the reports, although treatment by ACE inhibitors and ARBs in DM patients is associated with elevated levels of ACE-II, the treatment should be continued (9).

β Cell autoimmunity in recent respiratory infection

T1DM is an autoimmune disease. One of the important immunologic markers is pancreatic beta-cell autoantibodies (10). A previous study mentioned the higher risk of β-cell autoimmunity in patients with a recent respiratory infection. They showed that 5.6% of patients had persistent pancreatic islet autoimmunity (11, 12). It is noteworthy that about half of the non-diabetic COVID-19 patients experience hyperglycemia due to endogenous stress-induced glucocorticoid hypersecretion. So, COVID-19 may cause transient impairment of pancreatic islets cells' function (13). COVID-19 can also induce new-onset DM as permanent type damage in the pancreas. This type of cross-reactive antibody production against β cells can occur due to viral epitopes sharing homology to amino acid sequences of autoantigens. Cytokine release and T cell activation by a viral infection can raise the occurrence of T1DM in genetically predisposed individuals, and consequently, viral infections trigger autoimmune insulitis (8, 9). Glycosylation of ACEII receptors can be boosted by hyperglycemia and lead to insulin-dependent DM. Data showed frequent cases of severe DKA and insulin deficiency at the hospital admission, possibly because of β cell damage by the virus (7, 13).

Possible mechanism of increasing the risk of COVID-19 in DM patients

There are different mechanisms for increasing the risk of COVID-19 in DM patients, including the release of tissue injury-related enzymes, cytokine storm, hypercoagulability, and dysregulation of glucose metabolism (5, 14). Hyperglycemia is hazardous and highly frequent because its control by herbal and chemical drugs is difficult (15). Also, based on its mechanism, it can increase the activity of COVID-19. Obesity is a risk factor for DM and hyperglycemia (16). So, severe COVID-19 was reported due to its co-occurrence with DM (17).

Should clinicians discontinue ACE inhibitors and statins?

Initially, in the outbreak of COVID-19 and when researchers defined ACE-II as an essential receptor, confusion occurred about using ACE inhibitors because of their potential effects on the up-regulation of ACE-II receptors (18). Despite the controversial results regarding the continuing or stopping of ACE inhibitors and ARBs and the need for further research, several studies showed the beneficial effects of these medications on cardiovascular, renal, and pulmonary functions during COVID-19 (19, 20). Therefore, it is better to continue administering antihypertensive regimens, such as ACE inhibitors and ARBs, for these patients (7).

Although high lipids such as low-density lipoprotein or lipoprotein(a) may diminish ACE-II, statins, with their anti-inflammatory effects, lead to the up-regulation of ACE-II and neutralize this effect (7, 21). Statins should be continued because ACE-II expression is associated with a higher mortality rate, and discontinuation may lead to cytokine storm by increasing the interleukin 6 and 18. On the other hand, it is crucial to control lipid levels in COVID-19 because of the significant association between DM and cardiovascular diseases (7).

Vitamin D in COVID-19 in children with DM

It seems that vitamin D deficiency is a key factor in the initiation and spread of the COVID-19. Vitamin D supplementation can decrease the risk of infection and the mortality associated with COVID-19. The protective effect of sufficient vitamin D on pneumonia and lung damage could result from increasing the anti-inflammatory and decreasing the proinflammatory cytokines. It modulates the expression of ACE-II in lung tissues. Vitamin D may decrease interleukin-6 and interferon γ, which are the important predictors of worse outcomes in severe COVID-19 (22). In children, 2000 IU/d of vitamin D for 6 to 12 weeks and 600-1000 IU/d as the maintenance dose are recommended to correct vitamin D deficiency (<20 ng/mL). Previous results reported that vitamin D concentrations of ≥38 ng/mL cause a two-fold reduction in the risk of respiratory infections and duration of sick days (23).

Sick day management in COVID-19

In the pandemic of COVID-19, DM patients are recommended to be managed at home due to the imposed superinfection in hospitals. In COVID-19 diabetic patients, sick day rules included repeated blood glucose (BG) and urine or blood ketone assessments. Insulin use should not be stopped, and parents should have backup insulin at home, notice dehydration, and treat symptoms such as fever.

When vomiting prolongs for more than 4-6 hours and ketone levels in blood or urine are not reduced despite the mentioned sick day rules, the patient needs medical attention. During the COVID-19 pandemic, clinicians prefer to justify BG levels between 110 and 180 mg/dL (7).

When the child feels sick, and there is no ketone in the urine or BG is less than 250 mg/dL, sugar-containing fluids in small amounts (at least 100 mL/h) should be administered to keep up BG level and decrease the risk of starvation ketosis. In patients with minor illnesses without urine ketone, BG and ketone should be monitored every 2 to 4 hours. When BG is above 250 mg/dL, the sugar-free fluid should be administered (7). In sick day management of COVID-19 in other cases, patients should be managed based on Table 1.

management in COVID-19 for diabetic patients

Clinicians should consider some important points for DKA management during the outbreak of COVID-19. In mild DKA, patients are managed like sick day management. Although they should be managed in hospitals, they can be managed at home. In moderate to severe DKA, it is better to start intravenous (IV) fluid therapy from the beginning. Besides, during COVID-19, it is better to administer subcutaneous insulin instead of infusion regarding the importance of social distancing. Severe DKA in COVID-19 patients should be managed in ICU with access to IV infusion of fluid. If the patient has a perfusion disorder, intramuscular injection is needed due to insulin resistance consequent from COVID-19; after DKA, the patient can be managed by insulin up to 4 U/kg (24, 25).

Table 1. Sick day management of COVID-19 in other caSES

Urine Ketone Status	Glucose Testing and Extra Rapid-acting Insulin		Comment
	Insulin	Correction doses	
Negative or small	q2 hours	q2 hours for glucose >250 mg/dL	Check ketones every other void
Moderate or large	q1 hour	q1 hour for glucose >250 mg/dL	Check ketones in each void. Go to the hospital if emesis occurs

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Advice for possible hospital referral

Possible hospital referral is indicated in the following cases: a new diagnosis of T1DM; very young children (<5 years) with persistent fever; persistent vomiting for more than 2 hours; potential circulatory compromise; fruity breath odor; the presence of signs of exhaustion, confusion, abdominal pain or fast breathing; seizure; declining renal function, raised potassium, low sodium; the necessity for physical examination (foot ulcer, infection); recurrent severe hypoglycemia; HbA1c >11%; inability to eat or drink for more than 6 hours; inability to control BG or ketone; inability to keep BG above 70 mg/dL (8, 24, 25), pH <7.0, bicarbonate < 10 mmol/L, potassium < 3.5 mmol/L, high BG level for more than 24 hours despite extra insulin; persistent elevation of blood ketones >1.5 mmol/L or large urine ketone levels despite use of correctional doses of insulin and hydration after 4-6 hours; and continued weight loss (7, 14).

Hospital management

In hospitalized patients with T1DM and COVID-19, the clinicians try to avoid hyperglycemia and hypoglycemia as manifestations of the poor prognosis. Therefore, blood sugar in mild COVID-19 children is slightly more stringent compared to the non-sick state (26, 27).

COVID-19 and electrolyte dysregulation

Severe hypokalemia is more common in COVID-19 than in isolated DKA patients because when the virus binds to the ACE-II receptor, the down-regulation of the receptor and the reduction of aldosterone degradation lead to hypokalemia (28, 29). Besides, hypophosphatemia is prevalent in patients with DKA. As it may worsen neuromuscular weakness and respiratory failure, phosphate replacement is more advisable (30).

3. Conclusion

Regarding the outbreak of COVID-19 and its effects on different diseases, especially DM in children, it seems mandatory to consider T1DM and its consequences in children with COVID-19. Understanding their combined pathophysiology and mechanism is helpful for better management of the comorbidity. These considerations can help clinicians make better decisions about the treatment modalities, sick day management, and DKA treatment.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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