Abstract

Context: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection normally damages the respiratory system but might likewise impair endocrine organs’ function. Thyroid dysfunction and hyperglycemia are common endocrine complications of SARS-CoV-2 infection. The onset of type 1 diabetes (T1D) and associated complications, including diabetic ketoacidosis (DKA), hospitalization, and death, are thought to have increased during the coronavirus disease 2019 (COVID-19) pandemic. The aim of this study was to review the available data about the incidence rate of T1D and accompanying complications since the beginning of the COVID-19 pandemic.

Evidence Acquisition: A literature review was conducted using the electronic databases PubMed and Google Scholar. The keywords “T1D, T1DM, Type 1 DM or Type 1 Diabetes”, “Coronavirus, SARS-CoV-2 or COVID-19” were used to search these databases. Titles and abstracts were screened for selection, and then relevant studies were reviewed in full text.

Results: A total of 25 manuscripts out of 304 identified studies were selected. There were 15 (60%) multicenter or nationwide studies. The data about the incidence rate of T1D, hospitalization, and death are not consistent across countries; however, DKA incidence and severity seem to be higher during the COVID-19 pandemic. The present study’s data collection demonstrated that COVID-19 might or might not increase the incidence of T1D. Nevertheless, it is associated with the higher incidence and severity of DKA in T1D patients. This finding might indicate that antivirals are not fully protective against the endocrine complications of SARS-CoV-2 infection, which promotes the application of an alternative approach.

Conclusions: Combining medications that reduce SARS-CoV-2 entry into the cells and modulate the immune response to infection is an alternative practical approach to treating COVID-19.

Keywords: ACE2, DKA, SARS-CoV-2, T1D

1. Context

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a prominent global health concern. Severe acute respiratory syndrome coronavirus 2 is a ribonucleic acid (RNA) virus belonging to the family Coronaviridae. There are different variants with unique mutations, which mainly affect the respiratory system but can also damage the nervous system and endocrine organs. The clinical manifestations of COVID-19 vary from asymptomatic or mild disease to acute respiratory distress syndrome (ARDS), hospitalization, and death (1). The commonly reported endocrine complications are thyroid dysfunction and hyperglycemia (2). The connection between COVID-19 and endocrine disorders, such as diabetes mellitus (DM), is a nuanced area of research.

Diabetes mellitus is a metabolic disorder characterized by a defect in insulin secretion, insulin function, or both, causing hyperglycemia and other debilitating complications, including micro- and macro-vascular complications. The two main classifications of DM, namely type 1 diabetes (T1D) and type 2 diabetes (T2D), differ in that T1D consists of reduced insulin production; nevertheless, T2D consists of inadequate cellular response to insulin signaling (3). Coronavirus disease 2019 can
potentially increase the incidence rate of T1D and T2D. Type 1 diabetes typically begins with immune-mediated damage to pancreatic cells, which is triggered by genetic or environmental factors. Viral infections, such as enteroviruses and respiratory viruses, are probably responsible for autoimmunity against β-cells (4, 5). Generally, COVID-19 and T2D appear to have a bidirectional relationship; however, the relationship between COVID-19 and T1D remains controversial and multi-faceted (6).

Diabetic ketoacidosis (DKA) is a life-threatening complication that usually occurs in patients with T1D. In T1D, the absence of insulin promotes an excess breakdown of fats as an alternative source of energy, resulting in the buildup of acidic ketones and disrupting organ functions. During the COVID-19 pandemic, there was a notable increase in the incidence and severity of DKA in patients with T1D, suggesting a possibility that COVID-19 and DKA are causally connected (7-9). However, other studies found no evidence of a physiological association between DKA and SARS-CoV-2, implying that the surge in the incidence and severity of DKA during COVID-19 is best attributed to a diminished quality of care for diabetic patients due to an overburdened healthcare system (10-12). Moreover, although the severity of symptoms of T1D might have been exacerbated during the pandemic (once again, arguably due to strains on the healthcare system), the overall incidence rate of T1D might not have necessarily been impacted (13). Therefore, the interplay between COVID-19 and T1D is rather complex.

Although several systematic reviews have reported that SARS-CoV-2 infection can increase the risk of new-onset type 1 diabetes (NT1D) (14-17), no alternative approach was proposed to reduce the endocrine complications of COVID-19. This review aims to elucidate the intricate relationship between COVID-19 and T1D, emphasizing the different aspects of epidemiology, complications, and possible therapeutic strategies to improve their outcomes and mitigate mortality and morbidity associated with both diseases.

2. Evidence Acquisition

2.1. Data Sources and Searches

According to PRISMA guidelines (18), a systematic search was conducted in PubMed and Google Scholar for relevant studies. Search dates were within January 2020 and May 2023. The following keywords were applied for search: “T1D, T1DM, Type 1 DM or Type 1 Diabetes, Coronavirus, SARS-CoV-2 or COVID-19”.

2.2. Study Selection

Two authors (KK and NA) reviewed abstracts, and a third author (KA) made a cross-check. The references of relevant reviews were reviewed to include further potentially relevant articles. Two authors contributed independently to the selection process, data extraction, and data collection. The participants, study type, outcomes, and interventions were used to select the relevant studies. The selected studies were discussed to resolve disagreements, and a third author participated if needed. This study reviewed (1) clinical research articles, such as cohorts, cross-sectional studies, case-control studies, and case series, (2) review articles, including mini-reviews, systematic reviews, and meta-analyses; and (3) opinion and commentary articles, such as editorials, commentaries, perspectives, and letter to editors, that discuss the incidence, clinical characteristics, outcomes, complications, morbidity, and mortality of T1D in COVID-19 patients or vice versa. This study included multicenter, nationwide, or observational original studies that were cohort, cross-sectional, or case-control and reported the complications or incidence of NT1D during the COVID-19 pandemic. This study also reviewed the data from two systematic reviews by Nassar et al. (14) and D’Souza et al. (17). Three reviewers (KK, NA, and KA) evaluated the risk of bias in the selected studies to make sure cohort, cross-sectional, or case-control studies were included. Figure 1 shows the flowchart for the systematic review.

Duplicates were eliminated after a review of all recognized articles from the initial searches. The remaining papers were read in full. The publications were summarized in terms of the author, journal, year of publication, country of origin, study design, number of participants, type of intervention, age, gender, outcomes (e.g., death, DKA, or other complications), new-onset diabetes or worsening of pre-existing diabetes, and other results in general. Most studies were observational or nonrandomized studies. This study assessed the risk of bias and quality by producing review-specific questions and guidance, constructing a flow diagram for the study, and judging bias and applicability. A formal narrative data synthesis was performed to investigate the effects of COVID-19 infection on the incidence of T1D and associated complications (e.g., DKA and death). The consistencies or discrepancies among the studies were discussed.

3. Results

A total of 304 studies were found during the initial database searches. The exclusion process resulted in 25 eligible manuscripts for further investigation (7-13,
Tables 1 and 2 show summaries of the baseline characteristics of the included studies.

Study Characteristics. Among the 25 eligible studies, there were 15 (60%) multicenter or nationwide studies (7, 10, 11, 13, 19, 20, 24, 26, 28, 30, 31, 33-36). New-onset type 1 diabetes incidence was reported in 13 manuscripts (52%) (8, 10, 13, 20, 21, 23-27, 32, 35, 36) from countries other than Hungary (37) and Turkey (38), which are not included in Table 1. Eighteen studies reported DKA incidence or severity (7-13, 21-27, 29, 30, 32) during the COVID-19 pandemic. However, there was no increase in DKA incidence in autoantibody-negative T1D in Germany (10) or in NT1D in Israel (21). There was also no increase in severe DKA in Israel (21) and no increase in DKA or severity in the USA (29).

Clinical Outcomes and Complications of T1D Patients During COVID-19. Diabetic ketoacidosis, hospitalization rate, and death were studied in the selected studies. Diabetic ketoacidosis incidence, prevalence, or severity were increased in most studies (7-9, 11-13, 21-27, 30, 32) during the COVID-19 pandemic. However, there was no increase in DKA incidence in autoantibody-negative T1D in Germany (10) or in NT1D in Israel (21). There was also no increase in severe DKA in Israel (21) and no increase in DKA or severity in the USA (29).

The hospitalization rate of NT1D during the pandemic appeared to be stable in France (31). However, the data regarding the death rate is inconsistent, as increases in death were reported in China (9), England (33, 34), and the USA (28, 30); however, no increase in death was observed in France (19).

4. Discussion

In this narrative review, most studies reported an increase in DKA incidence and severity during the COVID-19 pandemic. Diabetic ketoacidosis is a serious...
complication of diabetes, which is associated with more severe pancreatic β-cell destruction and increased morbidity and mortality (39). There is generally a slight increase in the prevalence of DKA at the onset of T1D, which is estimated to be around 29.9%. However, the prevalence of DKA varies across the countries with the lowest prevalence, namely Sweden (19.5%) and Denmark (20.7%), and the highest prevalence, namely Luxembourg (43.8%) and Italy (41.2%) (40). Furthermore, the overall incidence of DKA is declining in Denmark (41) but increases through adolescence in England and Wales (42). Therefore, the incidence and severity of DKA could be additionally affected by COVID-19, which resulted in a relatively consistent increase in DKA incidence and severity across countries (Table 2) during the COVID-19 pandemic. This potentially underscores the underlying COVID-19-related mechanisms, including multisystem inflammatory response (43) and the exacerbation of insulin resistance (44). Additionally, the delayed diagnosis and heterogeneous presentation of NT1D during the COVID-19 pandemic could be further contributing factors (45).

Severe acute respiratory syndrome coronavirus 2 enters human cells mainly through the angiotensin-converting enzyme 2 (ACE2) receptor. There are other receptors that might mediate SARS-CoV-2 entry into human cells, including dipeptidyl peptidase 4 (DPP-4 or CD26), CD47, neuropilin-1, lectins, CD209L, and tyrosine-protein kinase receptor UFO (AXL). The host proteases, such as transmembrane protease serine 2 (TMPRSS2), furin, trypsin, elastase, and cathepsin L, are also involved in the process of SARS-CoV-2 entry into cells. Angiotensin-converting enzyme 2 on cell membrane has other responsibilities against inflammation, proliferation, and fibrosis.

The disintegrin and metalloproteinase domain-containing protein 17 (ADAM17) are indirectly involved in the process of SARS-CoV-2 entrance and tissue damage by shedding ACE2 from the cell membrane (46-48). Angiotensin-converting enzyme 2 expression in the gastrointestinal (GI) tract and pancreas is relatively remarkable. It is also expressed in essential metabolic tissues, such as the liver, kidney, adipocytes, and vasculature (49). Coronavirus can potentially target the metabolic tissues, especially the pancreas, which leads to islet cell damage (50), insulin resistance (51), and hyperglycemia (Figure 2).

The current information regarding the incidence of NT1D in children during the pandemic is not consistent across countries. This could be due to differences in the outcomes of treatment modalities, accessibility to effective treatment, and speed of conducting a successful
Figure 2. Illustrating the Cascade of Events Triggered by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection, Which Results in Reduced Insulin Production, Increased Insulin Resistance, and Hyperglycemia

The cascade of events triggered by SARS-CoV-2 infection can be summarized as follows:

1. **Insulin Resistance**: This can be caused by various factors including:
   - Increase in angiotensin II activity
   - Hyperinflammation
   - Hypercoagulability
   - Multi-systemic inflammatory response and oxidative stress
   - Impairment of insulin activity

2. **Hyperglycemia**: Induced by:
   - RAAS activation
   - Loss of ACE2 on cell membrane
   - Downregulation of ACE2 expression
   - Inflammation and immune activation

3. **Insulin Production**: Impaired due to:
   - Endothelial damage
   - Microvascular damage
   - Thrombosis
   - Fibrosis

4. **Autoimmunity against Beta-cell**
   - Autoantibodies
   - Loss of immune tolerance
   - Permanent inflammatory response

5. **Direct Damage**
   - From SARS-CoV-2 infection

6. **Indirect Damage**
   - Resulting from immune dysregulation

Severe acute respiratory syndrome coronavirus 2 can directly infect beta-cells and reduce beta-cell function. Moreover, SARS-CoV-2 infects and replicates in other tissues, such as the kidney, adipose tissue, liver, muscle, bone, and vessels, which causes inflammatory responses, cytokine storms, and multiorgan dysfunction. This, in turn, is associated with insulin resistance, dysglycemia, and even stress hyperglycemia with severe illness. The consequences of these events will increase SARS-CoV-2 infectivity and the risk of further organ damage. Created with BioRender.com.
also shown to reduce COVID-19 infectivity and severity in cirrhotic patients (67).

Antiandrogens downregulate TMPRSS2 and ACE2, which reduce SARS-CoV-2 entry into the cells (68). They lower the mortality, hospitalization rate, and duration of SARS-CoV-2 infection (69). Spironolactone, an aldosterone receptor antagonist with anti-androgenic effects, antagonizes TMPRSS2 and ADAM17, reduces virus entry into the cells, and diminishes SARS-CoV-2-mediated endothelial damage (70, 71). It has been reported that spironolactone improves clinical scores and reduces mortality, ICU admission, intubation, and end-organ damage in hospitalized COVID-19 patients (71).

Metformin activates AMP-activated protein kinase (AMPK), which leads to the phosphorylation of ACE2. Angiotensin-converting enzyme 2 phosphorylation enhances ACE2 stability on the cell membrane, increases Ang(1-7) and endothelial nitric oxide synthase bioavailability, and thereby provides lung protection by preserving endothelial function. Additionally, the phosphorylation of ACE2 might affect virus entry into the cells. Metformin also inhibits the mammalian target of the rapamycin (mTOR) pathway and modulates the immune response against the infection (72-74). Generally, metformin seems to be helpful in reducing SARS-CoV-2-related tissue injury. Metformin could not improve the clinical outcomes of COVID-19 patients impressively (75); however, it could reduce the incidence of long COVID (76). Dipeptidyl peptidase 4 inhibitors have immunomodulatory roles and possibly blunt the alternative route of virus entry through DPP-4 receptors (47). They can alleviate SARS-CoV-2 cytokine storm and injury to the organs. The use of DPP-4 inhibitors in patients with SARS-CoV-2 infection was associated with the improvement of glucose levels in diabetic patients and clinical improvement and reduction of inflammatory markers in diabetic and non-diabetic patients (71, 77, 78).

There are some limitations in the current systematic review. This study did not review all resources and did not have information from all areas of the world, which technically limits the applicability of the results for the missing regions of the world. In addition, the time of data collection during the pandemic is not similar in all studies, and it is possible that the incidence of T1D was transiently affected during the pandemic. However, in a meta-analysis by D’Souza et al. (17), there was a higher incidence rate of T1D during the first year (incidence rate ratio [IRR] = 1.14; 95% CI: 1.08 - 1.21) and second year (IRR = 1.27; 95% CI: 1.18 - 1.37) of the pandemic than the period before the pandemic.

4.1. Conclusions

Based on the collected evidence, the effect of SARS-CoV-2 infection on the incidence of NTID is controversial. However, COVID-19 increases the incidence and severity of DKA in T1D patients. Antivirals seem to be helpful but not completely protective against SARS-CoV-2-induced tissue injuries. An alternative therapeutic approach includes targeting the SARS-CoV-2 receptor, blocking virus entry, and alleviating inflammation, especially by combining medications with different beneficial characteristics, to tackle SARS-CoV-2 infection and associated complications. Flooding the path for future clinical trials to investigate the protective role of this alternative approach would be reasonable, as it is shown that the combination of spironolactone and sitagliptin could reduce the hospitalization rate and duration of the disease (79).

Footnotes

Authors’ Contribution: Kebria Kashfi and Narges Anbardar reviewed the literature and helped with writing. Kamyar Asadipooya reviewed the literature and wrote the manuscript. Artin Asadipooya helped with writing and editing.

Conflict of Interests: The authors declared that no conflict of interest exists.

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References


Table 1. Outcomes and Population of Included Studies with Type 1 Diabetes (T1D) and Coronavirus Disease 2019 (COVID-19) Listing the Countries in Alphabetical Order

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design and Population</th>
<th>Sample Size</th>
<th>Age</th>
<th>Gender (Male), No. (%)</th>
<th>Death, DKA, or NT1D</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birkebaek et al.</td>
<td>Multicenter study, children and adolescents diagnosed with T1D (1,179,769 children and adolescents)</td>
<td>2020: 3,198 in 2020; 1,041 in 2021</td>
<td>0.9</td>
<td>40-55</td>
<td>33.45 (10.25 DKA at T1D diagnosis)</td>
<td>No significant increase in the prevalence of DKA during the COVID-19 pandemic.</td>
</tr>
<tr>
<td>Lawrence et al.</td>
<td>Multicenter cohort study, children &lt; 18 years with the initial diagnosis of T1D</td>
<td>2020: 8,209 in 2020; 2021: 8,853 in 2021</td>
<td>0.8</td>
<td>27</td>
<td>715 DKA, 45 severe DKA, 5 NT1D</td>
<td>No significant increase in the severe DKA at the presentation of NT1D during the COVID-19 pandemic.</td>
</tr>
<tr>
<td>Bibet et al.</td>
<td>Multicenter cohort study, hospitalised patients with COVID-19</td>
<td>2020: 4,562 NT1D, 39 T1D; 2021: 3,238 NT1D, 2,903 T1D</td>
<td>0.6</td>
<td>0.005</td>
<td>0.004</td>
<td>No significant increase in severe DKA. No difference in severe DKA between 2020 and 2021.</td>
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<tr>
<td>Holman et al.</td>
<td>Population-based cohort study</td>
<td>2020: 194,680 (55.6)</td>
<td>0.6</td>
<td>0.13</td>
<td>0.13</td>
<td>No significant increase in severe DKA. No difference in severe DKA between 2020 and 2021.</td>
</tr>
<tr>
<td>Barron et al.</td>
<td>Multicenter cohort study,German Diabetes Registry, T1D incidence in children, adolescents, and young adults during the pandemic</td>
<td>2020: 2,740 NT1D; 2019: 2,903 T1D; 2018: 2,903 T1D</td>
<td>0.6</td>
<td>0.005</td>
<td>0.004</td>
<td>No significant increase in severe DKA. No difference in severe DKA between 2020 and 2021.</td>
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<tr>
<td>Cariou et al.</td>
<td>Multicenter observational study, diabetes patients hospitalized for COVID-19</td>
<td>2020: 4,562 NT1D, 39 T1D; 2021: 3,238 NT1D, 2,903 T1D</td>
<td>0.6</td>
<td>0.13</td>
<td>0.13</td>
<td>No significant increase in severe DKA. No difference in severe DKA between 2020 and 2021.</td>
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<tr>
<td>Madier et al.</td>
<td>Nationwide retrospective cohort study in three periods: week 2 of 2019 to week 12 of 2020, weeks 12-19 of 2020 to week 52 of 2021 (after lockdown)</td>
<td>2020: 261,456 T1D</td>
<td>0.7</td>
<td>0.005</td>
<td>0.004</td>
<td>No significant increase in severe DKA. No difference in severe DKA between 2020 and 2021.</td>
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<tr>
<td>Kamrath et al.</td>
<td>Multicenter cohort study, German Diabetes Registry, T1D incidence in children, adolescents, and young adults during the pandemic</td>
<td>2020: 2,903 T1D; 2019: 2,903 T1D; 2018: 2,903 T1D</td>
<td>0.6</td>
<td>0.13</td>
<td>0.13</td>
<td>No significant increase in severe DKA. No difference in severe DKA between 2020 and 2021.</td>
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<tr>
<td>Kamrath et al.</td>
<td>Multicenter Diabetes Prospective Study, German Registry</td>
<td>2020: 2,903 T1D; 2018: 2,903 T1D</td>
<td>0.6</td>
<td>0.13</td>
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<td>Kamrath et al.</td>
<td>Multicenter Diabetes Prospective Study, German Registry</td>
<td>2020: 2,903 T1D; 2018: 2,903 T1D</td>
<td>0.6</td>
<td>0.13</td>
<td>0.13</td>
<td>No significant increase in severe DKA. No difference in severe DKA between 2020 and 2021.</td>
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<tr>
<td>Study</td>
<td>Design and Context</td>
<td>Baseline Characteristics</td>
<td>Follow-up Characteristics</td>
<td>Results</td>
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<tr>
<td>Mastromarco et al. (25)</td>
<td>Retrospective, Pediatric and Melinos et al. TID Group (2005-2020) group 2019-2020</td>
<td>122 NT1D, 32 group 1, 46 group 2</td>
<td>9.1 ± 8.4</td>
<td>DKA (2.25 ± 0.45) vs. 2.25 ± 0.45; Severe DKA (0.1 ± 0.01) vs. 0.05 ± 0.01; Significant increase in DKA and severe DKA during the pandemic</td>
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<tr>
<td>Dargel et al. (27)</td>
<td>Observational retrospective cohort study children 0-18 years with newly diagnosed TID</td>
<td>34 group 2019, 52 group 2020 in March-May</td>
<td>9.9 ± 8.9</td>
<td>No significant increase in NTID and severe DKA during the COVID-19 pandemic period; DKA (2.25 ± 0.45) vs. 0.05 ± 0.01; Significant increase in DKA and severe DKA in NT1D children during the COVID-19 pandemic</td>
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<tr>
<td>Heer et al. (9)</td>
<td>Retrospective study, &lt; 15 years, NTID during the pandemic: March 17 to August 15, 2020</td>
<td>NT1D 107 (March-June 2020)</td>
<td>9.6 ± 8.4</td>
<td>Increase in the DKA rate has increased by 12%. Severe DKA cases noted in newly diagnosed TID children</td>
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<tr>
<td>Zubikiewicz &amp; al. (10)</td>
<td>Multicenter retrospective study, the TID pediatric registry for newly diagnosed TID</td>
<td>March 17 to August 15, 2020 vs. 2019</td>
<td>9.90 ± 8.77</td>
<td>Significant increase in DKA and severe DKA in NT1D children during the COVID-19 pandemic period; Increase in IR of T1D 2000-2019: 10.43/100,000/year in 2000; 22.06/100,000/year in 2019; Highest T1D incidence rate in January and February; DKA incidence: 36.67% in 2020 vs. 31.75% in 2019 (P = 0.0262)</td>
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<tr>
<td>Pietrakiet et al. (14)</td>
<td>Multicenter center study, DKA incidence TID COVID-19 (2019) vs. group 2020</td>
<td>1742 TID, 1247 (35%)</td>
<td>9.5 ± 8.63</td>
<td>Statistical difference in the frequency of DKA and severe DKA during the COVID-19 pandemic</td>
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<tr>
<td>Boboc et al. (25)</td>
<td>Observational retrospective cohort study, TID patient from Marie Curie Emergency Children’s Hospital, Bucharest</td>
<td>174 TID (March-June 2020)</td>
<td>7.59 ± 8.45</td>
<td>An increase in the incidence and severity of TID in children during the COVID-19 pandemic; 30.08% increase in NT1D during the pandemic; 67.40% increase in DKA incidence during the pandemic</td>
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<tr>
<td>Alagiri et al. (26)</td>
<td>Multicenter retrospective cohort study children 0-18 years admitted with NTID or DKA during the COVID-19 pandemic</td>
<td>100 (March-June 2020)</td>
<td>10 ± 8.45</td>
<td>Increase in IR of T1D from 17.27/100,000/year in 2020 to 25.90 cases/100,000 in 2020/2021; COVID-19 associated with an increase in the frequency of DKA in T1D</td>
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<tr>
<td>Dilek et al. (27)</td>
<td>Cross-sectional study, newly diagnosed with TID in Gaskara University hospital</td>
<td>74 (March-June 2020)</td>
<td>19 ± 8.34</td>
<td>Increase in the number of NTID, autoantibody positivity, rates, and severity of DKA during the COVID-19 pandemic</td>
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<tr>
<td>O'Malley et al. (29)</td>
<td>Multicenter cross-sectional, all patients &lt; 21 years of age with TID and COVID-19</td>
<td>101 March 1, 2020 - August 22, 2020</td>
<td>55.6% ± 48.5%</td>
<td>TID associated with a higher risk of morbidity and mortality in patients with COVID-19</td>
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<tr>
<td>Bogale et al. (28)</td>
<td>Retrospective analysis, all pediatric patients (age &lt; 18 years) newly diagnosed with TID</td>
<td>42 post-COVID</td>
<td>23.4 ± 8.53</td>
<td>Almost similar DKA rates and severity during COVID-19</td>
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<tr>
<td>Dam et al. (30)</td>
<td>Retrospective cohort, TID &lt; 21 years diagnosed 2020 May/June 2019-August/September 2019 and 2020</td>
<td>12,157 (M/J 2020)</td>
<td>4 ± 8.38</td>
<td>A significant rise in DKA rate and mortality during COVID-19</td>
<td></td>
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</tr>
</tbody>
</table>
| Trieu et al. (31)            | Hospitalized children with TID or TID and SARS-CoV,19 infection within April and November 2020 | 6 (36%)                   | 6 ± 8.38               | 16.3% increased rate of NTID in 2020; 8.5% decrease in NTID within 2020 to 2019; Increase in DKA incidence in 2020; 6 (36%)
Global Collaborative Network, 74 large healthcare organizations across 50 US states and 14 countries

1,091,494 pediatric COVID-19; 776,577 respiratory infections (not COVID-19)

9.3 NT1D 6 months after COVID; 72 (0.025%) NT1D 6 months after non-COVID-19 respiratory infection

Risk of NT1D after SARS-CoV-2 infection: 3 months: HR, 2.10 (95% CI: 1.48-3.00) 6 months: HR, 1.83 (95% CI: 1.36-2.44)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; DKA, diabetic ketoacidosis; IR, incidence rate; IRR, incidence rate ratio; IRT1D, incidence rate of type 1 diabetes; NT1D, new-onset type 1 diabetes; OR, odds ratio; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T1D, type 1 diabetes; T2D, type 2 diabetes

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