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The Pandemic (Covid-19) and Pediatric Diabetic Ketoacidosis: The Lessons We Have Learned

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ABSTRACT

In this review, we aim to outline the world's experience with pediatric diabetic ketoacidosis (DKA) during and after the recent pandemic due to Covid-19. Although most of the literature during the pandemic illustrated the devastation wreaked on adults with diabetes, it took its toll on the pediatric population as well. Here we describe the incidence, prevalence, global impact, and varied presentations of Covid-19 related DKA. We opine on the mechanism of action or pathophysiology of pandemic related DKA, from direct viral effects to indirect mechanisms, such as inability to seek medical help and/or fear of seeking help at medical establishments that crucially kept children away from care only to present in worse states of chronic disease. The silver lining was the advent of telehealth and treatment of DKA in non-traditional settings that ironically broadened the scope of care. Lastly, we review areas in need of future study so that we are better prepared as pediatric clinicians for the next pandemic to protect the children in a more thorough and durable fashion. There are numerous lessons we have learned from this that we can apply now in our daily practice to improve the care we give to our patients.

Introduction:

Anecdotally, as we experienced the Covid-19 (coronavirus disease 2019, caused by SARS-CoV-2 originating in Wuhan, China) pandemic in 2020, the pediatric endocrinology sector noted a distinct rise in pediatric diabetes (both type 1 and type 2 diabetes mellitus; T1DM and T2DM, respectively). Due to more frequent presentations of diabetes, we thus noted more frequent episodes of diabetic ketoacidosis (DKA); the latter were more severe in nature. In this review, we aim to explore this observation in the US and globally. Although many suggested that the pandemic did not affect the pediatric population, it clearly did in this realm. DKA, if not caught early can result in death. We describe here, the scope of the pandemic effects on pediatric diabetes and the serious, if not deadly consequences. The golden lining of the pandemic was the evolution of telemedicine which helped, but not enough (too little, too late). Telemedicine, in its infancy was very much brought to fruition in the fight to keep pediatric providers in touch with their patients who had access to the internet. In the future we will be better prepared to handle such large disruptions to the health system, particularly in this vulnerable pediatric population with chronic disease. It is important to document our cumulative experience now to inform healthcare providers in the future when this happens again. Let us learn our lessons today to help save lives and reduce morbidity and mortality in the future.

Incidence:

In a recent edition of *Pediatric Annals*, we showed that worldwide, the incidence of both T1DM and T2DM, or all cause pediatric diabetes had increased worldwide during and after the pandemic[1]. Furthermore, Rahmati, et al.[2] found that SARS-CoV-2 infection was associated with an elevation in the risk of DKA in children and adolescents compared with non-Covid-19 control groups "RR = 2.56, 95% CI 1.07-6.11, p = 0.03". Their findings were mainly obtained from US medical claims databases, and suggested that SARS-CoV-2 infection was associated with higher risk of developing new-onset T1DM and DKA in children and adolescents. These findings highlight the need for targeted measures to raise public health practitioners and physician awareness to provide intervention strategies to reduce the risk of developing T1DM in children and adolescents who had Covid-19. In 2020, Chao, et al.[3] demonstrated that youth with new-onset T2DM had a greater incidence of DKA at presentation than previously observed. They suggested that future studies should examine the impact of SARS-CoV2 exposure on the presentation of T2DM in all age-groups to inform better patient care and to determine which age groups were most susceptible. These were general observations.

Jaliliova, et al.[4] intimates in their 2023 study, that the rate of severe DKA, but not the overall rate of DKA increased during the Covid-19 pandemic compared to the prior four years. They believe this was due to the behavior of the parents of ill children and the limited access to the healthcare system. Despite this limited access, parental concern may have been sufficiently high to then seek medical attention for their children, avoiding the increased frequency of DKA as the first presentation of new-onset T1DM; the increase in severity of DKA was still unexplained in this study. Another study conducted in Alberta, Canada performed a chart review over the period of March 17, 2020 to August 31, 2020. This Canadian study group found that while the number of children presenting with T1DM was similar during the pandemic period compared to pre-pandemic, the frequency of DKA at diabetes onset was significantly higher in the pandemic period and incidence of severe DKA (with the possibility of death) was also higher[5]. A meta-analysis, that included 24 papers with a total of 124,597 children with diabetes, found that statistically significant increases in risk of DKA among newly diagnosed T1DM patients occurred during the pandemic "RR 1.41; 95% CI 1.19, 1.67; $p < 0.01$; $I^2 = 86\%$", especially in severe forms of DKA "RR 1.66: 95% CI 1.3, 2.11", when compared to before the pandemic. The meta-analysis further demonstrated that DKA in newly diagnosed children with T1DM had increased during the pandemic and presented with severe forms. This may reflect that Covid-19 may have contributed not only to the development but also the severity of DKA. This meta-analysis concluded that DKA, a life-threatening complication of T1DM, had indeed increased during the Covid-19 pandemic. These findings reflect that Covid-19 may have altered the presentation of T1DM that was somehow related to DKA severity[6].

The pandemic had a global impact as we know but this impact on DKA in children was noted all over the world. A study conducted in 47 pediatric diabetes centers caring for > 90% of youth in Italy found that the increase in frequency and severe of DKA in children with newly diagnosed T1DM during the Covid-19 pandemic in 2020, had no apparent association with the severity of Covid-19 infection nor containment measures. They conclude that there had been a silent outbreak of DKA in children during the pandemic, and preventive action was required to subvert this phenomenon in the event of further generalized lockdowns or future outbreaks[7].

Certain populations were disproportionately affected. One study in which retrospective data consisting of 27,292,879 patients from the US Cerner Real-World Data (nationwide cohort) were reviewed and showed that a Covid-19 diagnosis was associated with significantly increased risk of new-onset T1DM and American Indian/Alaskan Native, Asian/Pacific Islander, and Black populations were particularly at risk. In patients with pre-existing T1DM, the risk of developing DKA was significantly increased following a Covid-19 diagnosis[8]. DKA frequency increased among T1DM patients during Covid-19 surges with highest frequency among non-Hispanic Black patients in comparison to non-Hispanic White individuals. DKA was less common among patients using continuous glucose monitors (CGM) and/or insulin pumps. These findings highlight the urgent need for improved strategies to prevent DKA among patients with T1DM, not only under pandemic conditions, but under all conditions; especially among certain populations most affected by health inequities[9]. These studies link populations with lower income and poor access to healthcare with greater risk of DKA.

Lawrence, et al.[10] found that a significant increase in the frequency of severe DKA at presentation of T1DM was observed during the initial period of Covid-19 restrictions

and lockdown conditions. They further hypothesized that concern about presenting to the hospital during a pandemic led to a delay in diagnosis. These data have important implications for advocacy in seeking healthcare for non-pandemic-related conditions during a global pandemic. Adou et al.[11] also found an increase in the frequency of newly diagnosed cases that were identified during the first and the second Covid-19 waves compared with the pre-Covid-19 period. The patients presented with more severe DKA, probably due to a delay in presentation. The frequency of hypokalemia development was also significantly higher, likely due to the delay in presentation leading to a longer period of electrolyte loss. The severity of DKA was associated with a longer intensive care unit (ICU) admissions. They conclude that further studies are required to establish a definitive link between the Covid-19 pandemic and the severity of presentation. Both studies link the pandemic itself with severity of DKA.

Interestingly, some smaller case reviews found no difference in DKA pre- vs. post-pandemic. Donbaloğlu et al.[12] reported only 2 cases that tested positive for severe acute respiratory syndrome coronavirus 2 among new-onset T1DM patients during the pandemic in a Turkish population. Although they found an increase in the number of new-onset T1DM cases in comparison to the pre-pandemic period, rates of DKA and severe DKA were similar. There were no findings to suggest that severe acute respiratory syndrome coronavirus 2 took part in T1DM pathogenesis. Since the development of T1DM is a long process with autoimmune underpinnings that develops over months to years, they conclude that prospective studies were needed to investigate the long-term effects of severe acute respiratory syndrome coronavirus 2 on the development of T1DM and subsequent DKA.

As for T2DM and DKA, Chambers, et al.[13] in Arizona, found that there was a significant increase in T2DM cases that occurred following the onset of the pandemic with a greater risk of DKA and severe ketoacidosis leading to longer hospital stays and more intense critical support. Racial disparity was evident with a higher proportion of Black and American Indian children presenting with ketoacidosis following the pandemic onset in their T2DM cohort. Thus, severe DKA did not only present in T1DM but also in children presenting with T2DM.

Prevalence:

Pre-Covid-19 vs post-Covid-19, the prevalence of DKA, particularly in certain populations, increased as well. Ebekozien, et al.[14] examined whether DKA was more prevalent among Non-Hispanic (NH) Black and Hispanic patients with T1DM with laboratory-confirmed Covid-19 infections compared to NH Whites. They found that among T1DM patients with Covid-19 infection, NH Black patients were more likely to present in DKA compared with NH White patients. Their findings demonstrate additional risk among NH Black patients with T1DM and Covid-19. Nagl, et al.[15] analyzed the annual prevalence of new onset-DKA from 2012 to 2020 with a sub-analysis for the lockdown-periods during the Covid-19 pandemic in 2020. In this study, all newly diagnosed children with T1DM aged <15 years were prospectively registered in the population-based Austrian Diabetes Incidence Study. The annual DKA prevalence was analyzed using Joinpoint regression (a statistical method that identifies changes in population parameters over time). The DKA prevalence during the lockdown periods in 2020 and the corresponding periods in 2015-2019 were also examined. In the years 2012-2020 the mean prevalence of new onset-DKA in Austria was 43.6% and above the mean prevalence of previous decades (1989-2011) of 37.1 %. A particularly high prevalence was found among children <2 years of age “72.0% DKA, 32.8% severe DKA”. No significant gender difference was found. Prevalence of severe DKA at T1DM-onset increased significantly since 2015 “p = 0.023”. During the lockdown in 2020, 59.3% of children were diagnosed with DKA at T1D-onset, compared to 42.1% during the previous 5 years. Moreover, 20% of children had severe DKA at T1DM diagnosis, compared to 14% during the comparison period. The previously already high prevalence of DKA at T1DM-onset had further increased over time. They conclude that the Covid-19 pandemic had exacerbated the problem of a late or delayed diagnosis of diabetes in children, resulting in new onset-DKA.

Global Impact:

Increased DKA and severity not only affected the United States but was seen worldwide as previously noted. Let us explore the scope of these implications. The lockdown implemented in Saudi Arabia significantly impacted children with T1DM which led to an increased DKA frequency, including children with new-onset T1DM, potentially owing to delayed presentation[16]. A Finnish study demonstrated that more children with T1DM had severe DKA at diagnosis during the pandemic. They hypothesized that this was not a consequence of SARS-CoV-2 infection. Instead, it likely stemmed from delays in diagnosis following changes in parental behavior and healthcare accessibility[17]. Despite emerging evidence of increased pediatric T1DM and DKA worldwide following the Covid-19 pandemic, studies in Asia were lacking. Thus Lee, et al.[18] aimed to determine the frequency, demographics, and clinical characteristics of new onset T1DM during the pandemic in Malaysia. They found that new onset T1DM increased during the pandemic, with a greater proportion having severe DKA. They noted that more studies were needed to evaluate the mechanism leading to this rise in DKA to guide intervention measures.

The International Society for Pediatric and Adolescent Diabetes (ISPAD) investigated perceptions, challenges, and experience of health care professionals (HCP) taking care of children and young people with diabetes worldwide during Covid-19 pandemic. The ISPAD survey showed that many HCP adapted to the pandemic by resorting to telemedicine. One fourth of HCP reported delays in diagnosis and increased rates of DKA. The emergence of the Covid-19 pandemic had an important impact on family's behavior that may have led to an increase in DKA presentation and the evolution of telemedicine[19]. Although the latter was helpful it clearly did not mitigate the problem of diabetes complications arising during and after the pandemic.

A population-based study, the product of a national collaboration of Israeli pediatric diabetes centers,

investigated the presentation of childhood-onset T1DM. The frequencies of DKA and severe DKA observed during the Covid-19 period from March 15, 2020 until June 30, 2020 were compared with the same periods in 2019, 2018, and 2017 using multivariable logistic regression, adjusting for age, sex, and socioeconomic position. The dramatic increase in DKA they found at presentation of childhood-onset T1DM during the pandemic mandated targeted measures to raise public and physician awareness[20]. In Spain, a change in monthly distribution of cases (decrease in March presentation with more cases in May through November, which is opposite to the typical monthly or seasonal distribution) was described, with an increase in DKA at onset of T1DM. No differences were found in severity, although there were differences in the age distribution, with an increase in the number of cases in children under 4 years of age[21]. In Vojvodina, Serbia, the pandemic was associated with a higher incidence rate of T1DM, longer duration of symptoms of T1DM, a higher frequency of DKA, and more severe DKA at diagnosis. They found that patients aged 10–14 years (puberty, a time of increased insulin resistance) were a particular risk group for the occurrence of T1DM with severe clinical presentation. They note that additional studies were needed with a longer study period and in a wider geographical area, with data on exposure to Covid-19 infection, the permanence of new-onset T1DM, and the psychosocial impact of the pandemic[22]. In summary, the increased rate and severity of DKA in children was documented globally.

Presentations:

In our experience, not only did we note an increase in DKA but this was coupled with an increase in co-morbid complications such as acute respiratory distress syndrome (ARDS), multi-system inflammatory syndrome (MIS), hyperglycemic hyperosmolarity syndrome (HHS), general increase in severity of DKA presentation (higher blood glucose and hemoglobin A1C or HbA1C), T2DM with DKA, obesity and death. There was also an interplay between infection with Covid-19 and severity of DKA.

In general, age over 12 years and initial CRP were associated with need for pediatric intensive care unit (PICU) admission with Covid-19 infection at DKA presentation. Organ dysfunction was associated with elevated CRP on admission, elevated WBC, thrombocytopenia and DKA. These factors may be useful in determining risk for critical illness and organ dysfunction in pediatric Covid-19[23]. Multisystem inflammatory syndrome in children or MIS-C illness with purpura fulminans should be considered in children and adolescents presenting with complex multisystem involvement in this era of Covid-19 as we continue to manage diabetes with presence of this virus. Management with immunomodulatory agents were lifesaving[24].

Given that children with diabetes have increased risk of infection due to their hyperglycemic environment, we need to be cognizant of unusual infections in this cohort. Along the lines of rare co-morbidities, the occurrence of mucormycosis has been observed in individuals with Covid-19. However, there is limited information on the epidemiological factors, presentation, diagnostic certainty, and outcome of this infection in children. Manuscripts were systematically searched from December 2019 to March 2023 by Amaral, et al.[25]. They identified 14 cases of pediatric mucormycosis in patients with Covid-19. The median age of these patients was 10.7 years. Among these cases, 10 were associated with active Covid-19 infection. In 7 cases, the patients had pre-existing diabetes mellitus and concomitant DKA. Corticosteroids were administered to treat Covid-19 in 7 of the patients. The most common clinical presentation of the disease was rhino-orbital cerebral mucormycosis. Seven patients died “50%”. Given the high mortality rate, clinicians need to maintain a high level of clinical suspicion for mucormycosis in pediatric patients with DKA and Covid-19.

Obesity is a complicating factor in severity of presentation. As an increased body of Covid-19 related research is now available, it became apparent that the effects of Covid-19 extend beyond that of the respiratory system. Among others, the endocrine system is particularly vulnerable to perturbation from a Covid-19 infection. A review by Kostopoulou et.al[26], summarized the bidirectional relationship between COVID-19 and the endocrine system in children and adolescents, by describing both the possible susceptibility of children and adolescents without endocrinopathies to those with endocrine disorders (diabetes) following Covid-19 infection. They also note the potential susceptibility to Covid-19 infection and severe infection, or the aggravation of endocrine dysfunction in patients with pre-existing endocrine diseases. They show data that suggest both increased obesity and diabetes rates, as well as increased severity and frequency of DKA following Covid-19 infection, particularly in obese children. Conversely, patients with diabetes and obesity may experience a more severe course of Covid-19 infection. However, in most cases, children, and adolescents with well-managed and regulated endocrine disorders do not appear to be at increased risk of infection or severe infection from Covid-19. Thus, adhering to the appropriate "sick day management protocols", maintaining an adequate supply of medications and supplies, maintaining close contact with the therapeutic team, and seeking medical help without delay when needed, are the main recommendations for a safe outcome per this group. Additional lessons learned during the pandemic include the risk for mental health diseases. These are caused by the child’s disrupted routine due to Covid-19 related protective measures and the importance of adopting alternative communication options, such as telehealth visits, to ensure uninterrupted diabetes care.

Higher HbA1C levels of newly diagnosed patients presenting with DKA may have been associated with delayed admission to health institutions due to Covid-19 lockdowns and the length of insulin-free periods that were found to be longer, compared to those previously diagnosed patients with T1DM. Results from Varol, et al.[27], performed a retrospective analysis of 55 children aged 1 month to 18 years old, diagnosed with DKA, and followed at Istanbul Sehit Prof. Dr. Ilhan Varank Sancaktepe Training and Research Hospital PICU between April 2020 and December 2021, and found higher HbA1C levels in this population. They emphasized

the importance of physician's and family's awareness of the symptoms of diabetes in terms of making early diagnoses with prevention of DKA during the public health measures that were instituted during the COVID-19 pandemic and other lockdowns going forward. Monitoring of HbA1C is a good screening tool.

A significant increase in T2DM cases occurred following the onset of the pandemic with a greater risk of DKA and severe ketoacidosis as note previously by Chambers, et al. in 2022[13]. Another group, Shimony et. al[28], found that the incidence of T1DM hospitalizations did not increase during the pandemic; however, they tripled for T2DM patients. All new onset DM pediatric patients during the pandemic were more likely to present in DKA. Patients admitted with new onset T2DM were socioeconomically more vulnerable. For T1DM, the peak of local pediatric diabetes admissions in 2020 occurred slightly later coinciding with the reopening of primary care physicians (PCP) offices and schools.

Electrolyte disturbances in patients with DKA can increase the risk of cardiac arrhythmias. Despite the obvious correlation between these three, little has been reported about the co-incidence of these conditions: Covid-19, DKA and cardiac arrhythmias. In the case report by Howard, et al.[29], they describe two children with Covid-19, new-onset DKA and cardiac arrhythmias. These cases emphasize the importance of close cardiac and electrolyte monitoring in patients with Covid-19 infection with diabetes. Cardiac arrythmia can lead to death during DKA.

In a case study by Duong-Quy, et al.[30], they describe a patient that was diagnosed with Covid-19-induced ARDS associated with MIS-C secondary to acute respiratory failure, acute kidney injury, and new-onset T1DM with DKA. The patient was intubated for mechanical ventilation and received a normal saline infusion along with continuous insulin infusion (0.1 IU/kg/hr) for the treatment of his DKA (usual therapy). He was also treated with methylprednisolone, aspirin, and heparin, and underwent continuous renal replacement therapy for acute renal failure for nine days. The patient was discharged from the PICU on day 16 and was followed up as an outpatient with daily treatment, including subcutaneous insulin injections and a calcium channel blocker for hypertension. This illustrates the severity of DKA at the time of presentation during the pandemic and risk of death due to co-morbid conditions.

Little is known about the association between novel Covid-19 and T1DM in children. A 16-year-old female patient with a history of T1DM was admitted for life threatening DKA. She recovered from the DKA after 24 hours of insulin infusion and rehydration. On day 2, she was diagnosed with Covid-19. The DKA relapsed and required restarting of the insulin infusion. She developed leukopenia, neutropenia, and high ferritin. Upon recovery, she was discharged for self-quarantine. Severity of DKA in children with COVID-19 is multifactorial. Clinical suspicion of Covid should be heightened in patients with T1DM who present with unexplained severe DKA[31]. The interplay between covid-19 and DKA is still being investigated; severe DKA, think possible Covid-19 infection.

Although most children with Covid-19 are asymptomatic or have mild symptoms, many symptomatic children still require admission to the PICU. Multiple cases of DKA and hyperosmolar hyperglycemic syndrome (HHS) associated with Covid-19 have been reported in adults. However, to our knowledge, only few similar cases have been published in the pediatric population. Tseng, et.al[32] report one of the first few severe cases of mixed HHS with DKA associated with Covid-19 in an adolescent. Their patient was successfully treated with intravenous immunoglobulin, Remdesivir, and methylprednisolone. Fluids were provided via an HHS protocol; slow and not excessive, lowering glucose slowly to avoid cerebral edema. As the pandemic continues in its aftermath, clinicians should be aware of this syndrome and consider early use of Remdesivir and corticosteroids. Further studies are required to understand the pathophysiology of this syndrome occurring concomitantly with Covid-19 and alter fluid management accordingly.

Alizadeh, et al.[33], presents a novel case of a 16-month-old boy with a history of prematurity plus intrauterine growth restriction, severe failure to thrive, microcephaly, pachygyria, agenesis of the corpus callosum, and postnatal embolic stroke, who presented with new-onset diabetes mellitus and DKA in the setting of severe acute respiratory syndrome and Covid-19 infection. The course was complicated by atypical hemolytic uremic syndrome (aHUS). This patient demonstrated remarkable insulin resistance during the period before aHUS diagnosis, which resolved with the first dose of eculizumab therapy. There is increasing evidence that Covid-19 is associated with thrombotic disorders and that microangiopathic processes plus complement-mediated inflammation may be implicated. In this case report, they describe a pediatric patient with Covid-19 and a new complement-mediated microangiopathic thrombotic disease. Because whole-exome sequencing and extensive workup returned without a clear etiology for the aHUS, the authors presumed it was a Covid-19 triggered case of aHUS versus an idiopathic case that was unmasked by the infection.

As the incidence of pediatric DKA increased during the peak of the Covid-19 pandemic, the objective of the study by Azova, et.al[34], was to investigate whether rates of hyperosmolar therapy administration for suspected clinically apparent brain injury (CABI) complicating DKA increased during this period as compared to the three years immediately preceding the pandemic. They aimed to compare the characteristics of patients with suspected CABI before the pandemic, patients with suspected CABI during the peak of the pandemic, and those with DKA but without suspected CABI during the pandemic. Patients aged ≤18 years presenting with DKA before "March 11, 2017–March 10, 2020" and during the peak of the pandemic "March 11, 2020–March 10, 2021" were identified through a rigorous search of two databases. Predefined criteria were used to diagnose suspected CABI. Biochemical, clinical, and sociodemographic data were collected from a comprehensive review of the electronic medical record. The proportion of patients with DKA who received hyperosmolar therapy was significantly higher "$P = 0.014$" during the pandemic compared to the prepandemic period; however, this was only significant among patients with newly diagnosed

diabetes. Both groups with suspected CABI had more severe acidosis, lower Glasgow Coma Scale scores, and longer hospital admissions "$P < 0.001$ for all" than cases without suspected CABI. During the pandemic, the blood urea nitrogen concentration was significantly higher in patients with suspected CABI compared to those without suspected CABI, suggesting they were more severely dehydrated. The clinical, biochemical, and sociodemographic characteristics of patients with suspected CABI were indistinguishable before and during the pandemic. They conclude that administration of hyperosmolar therapy for suspected CABI was more common during the peak of the Covid-19 pandemic, possibly a result of delayed presentation, highlighting the need for increased awareness and early recognition of the signs and symptoms of diabetes and DKA, especially during future surges of highly transmissible infections.

More information is needed to understand the clinical epidemiology of children and young adults hospitalized with diabetes and Covid-19. Agathis, et al.[35] describe the demographic and clinical characteristics of patients <21 years old hospitalized with Covid-19 and either T1DM or T2DM during peak incidence of SARS-CoV-2 infection with the B.1.617.2 (Delta) variant. Their findings highlight the importance of considering diabetes in the evaluation of children and young adults presenting with Covid-19; the challenges of managing young patients who present with both Covid-19 and diabetes, particularly T2DM; and the importance of preventive actions like Covid-19 vaccination to obviate severe illness among those eligible, with both Covid-19 and diabetes. This study illustrates the importance of thinking about covid-19 when children present with diabetes of any type and the protective role of vaccination.

There is a mutual influence between Covid-19, diabetes ketoacidosis, and acute pancreatitis, with clinical manifestations overlapping each other, which can lead to misdiagnosis and delayed treatment that could aggravate the condition and affect the prognosis. Covid-19-induced DKA and acute pancreatitis are extremely rare, with only four case reports in adults and few to no cases yet reported in children. However, Liu, et al.[36] report a case of acute pancreatitis associated with DKA in a 12-year-old female child post coronavirus infection. The patient presented with vomiting, abdominal pain, shortness of breath, and confusion. Laboratory findings showed elevated levels of inflammatory markers, hypertriglyceridemia, and high blood glucose. The patient was treated with fluid resuscitation, insulin, antibiotics, somatostatin, omeprazole, low-molecular-weight heparin, and nutritional support. Blood purification (apheresis) was administered to remove inflammatory mediators. The patient's symptoms improved and blood glucose levels stabilized after 20 days of admission. This case highlights the need for greater awareness and understanding of the interrelated and mutually promoting conditions of Covid-19, diabetes ketoacidosis, and acute pancreatitis among clinicians, to reduce misdiagnosis and missed diagnoses.

As we know, DKA is a potentially life-threatening condition. Based on literature reviews, the risk of severity of DKA in children was significantly associated with Covid-19 cases during the first wave of the pandemic. This could be attributed to social distancing restrictions which delayed hospital presentation and timely treatment and interventions. Ashraf, et al.[37] presents a case of a 15-year-old female, with T2DM, who presented during the pandemic with severe DKA from another hospital. She had an elevated glucose level at home for three days that was worsening but parents managed the patient at home out of fear of the patient contracting Covid-19 if she was brought to the hospital. After she deteriorated, the parents took her to the nearest hospital which did not have a PICU. She was immediately transferred to a facility with a PICU. The patient was intubated immediately because of altered mental status possibly due to cerebral edema from severe metabolic acidosis and elevated glucose level. The patient rapidly progressed to shock, ARDS, and multiple organ dysfunction syndrome (MODS). She was managed aggressively with vasopressors, fluid resuscitation, and an insulin drip. She had four cardiac arrests for which she was resuscitated. Despite all efforts, she subsequently died less than 24 hours after admission to the PICU. The authors sought to shed light on an emerging phenomenon due to the pandemic, wherein due to the fear of contracting Covid-19, many parents opt to keep and manage sick children at home. This report highlights the important role that aversion to presenting to medical establishments out of fear of contracting Covid-19 may have led to the untimely and preventable death of this patient. It also outlines the importance of future educational reforms toward changing the patient and family's perception of hospitals and medical institutions, especially in children with pre-existing chronic medical conditions.

The Covid-19 pandemic affected the management and follow-up of many chronic ailments. Restricted access to healthcare and fear of contracting the virus during medical facility visits resulted in poor compliance, irregular follow-up visits, treatment, and delayed diagnosis of complications in pediatric diabetes such as DKA. As such, the incidence of complicated DKA in resource-limited settings was high due to delayed presentation, poor compliance with therapy, and associated comorbidities such as malnutrition, sepsis, and death. The increased surge in DKA, in the face of limited resources, prompted clinicians to find alternative solutions to manage these children effectively[38]. Overall, they found that rapid adoption of telemedicine significantly improved the follow-up needs and glycemic metrics in pediatric T1DM and coincidentally the prevention of DKA.

In a letter to the editor, regarding an editorial in the *Journal of Diabetes,* Foster, et al.[39] commented on the negative impacts of the Covid-19 pandemic on our healthcare system. They note that not only did rates of DKA at T1D diagnosis increase during the COVID-19 pandemic but severity of complications increased as well. They hypothesized that this was likely due to decreased healthcare access during the pandemic vs. actual Covid-19 infection, as limited access to care was a risk factor for DKA. This notion was supported by the small minority of new-onset T1DM patients with concomitant Covid-19, the knowledge that the development of autoimmunity in T1DM precedes presentation by months to years, and the absence of detectable SARS-CoV-2 proteins in the

endocrine cells of pancreata from people with Covid-19. The Network for Pancreatic Organ Donors with Diabetes (nPOD) is a program developed to procure and study pancreata and other tissues from cadaveric organ donors in different stages of T1DM. During the pandemic, nPOD had received two COVID-19 negative donors where the initial presentation of DKA was delayed, resulting in devastating outcomes and death. This demonstrates that death is a reality in DKA and covid health care restrictions likely resulted in deaths in children with T1DM vs. infection alone.

Pathophysiology:

The Covid-19 pandemic has introduced countless challenges to the medical field. Although pediatric patients have been reported to have lower rates of Covid-19 mortality, the presence of pre-existing conditions heightened the severity of their clinical presentation. A case report by Modarelli, et al.[40] discusses the potential influence Covid-19 might have on diabetic ketoacidosis. The patient, a 6-year-old girl with known T1DM, presented with acute onset of abnormal breathing and altered mental status. The day prior, she had 1 episode of emesis, diarrhea, and abdominal pain but no fever. She presented to an outside hospital and was reported to have agonal breathing with a Glasgow Coma Scale score of 8 (eyes open to pain, no verbal response to stimuli, and localized pain). She was promptly intubated. The initial laboratory tests revealed severe DKA. A family member had Covid-19, and she too tested positive for Covid-19. The patient's rapid progression and severity of illness required a discussion of how Covid-19 might affect diabetes and indicate opportunities for improving clinical practice in children with pre-existing diabetes. They discussed how Covid-19 might change the underlying pathophysiology of DKA and cause metabolic complications. Possible mechanisms include viral binding to angiotensin-converting enzyme 2 (ACE2) receptors thus enabling a proinflammatory "cytokine storm" leading to severe insulin resistance. Additionally, ketoacidosis and altered mental status have been present in patients with Covid-19 without underlying diabetes, which might potentiate the symptoms resulting in DKA. They conclude that prompt recognition of DKA is warranted, as caregivers may attribute the symptoms to Covid-19 rather than to DKA, resulting in an increased severity of illness on presentation with acute symptom onset, as described in this report.

Many studies described an increase in severity due to delay in diagnosis due to lockdowns. In particular, Dzygalo, et al.[41] concluded that during the pandemic lockdown resulting in changes in society and the health care system, that the DKA rate increased by 12 percentage points with more severe cases (higher HbA1C) noted in children with newly diagnosed T1D. Regular education of the society about the symptoms of diabetes would contribute to faster diagnosis of T1DM and reduction of DKA prevalence. Similarly, another group found the same phenomenon, that delay in diagnosis was found due to the lockdown implemented in Saudi Arabia[42] that had significantly impacted children with T1DM and led to an increased DKA frequency, including children with new-onset T1DM, likely owing to delayed presentation. Thus, the mere action of keeping people away from the healthcare system resulted in severity of presentations.

As to mechanisms, the in vivo and in vitro studies by Wu, et al.[43] revealed that factors such as direct viral damage, "metabolic dysfunction", and immune responses all were attributed to the process of T1DM after suffering from a Covid-19 infection. Furthermore, Keiner, et al.[44] showed results that suggest that infection with Covid-19 provokes a metabolic derangement, such as insulin resistance, over and above factors that typically contribute to pediatric DKA. These findings underscore the significant and direct threat posed by Covid-19 in pediatric T1DM and emphasize the importance of mitigation and monitoring, including vaccination as a primary prevention.

Children with hyperglycemic crisis (HGC or diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, or hyperosmolar ketoacidosis) had a higher severity of illness during the pandemic which was sustained over 2 years and a pathophysiologic mechanism. Reduction in social distancing and evolving variants of SARS-CoV-2 over the 2 years after the pandemic did not significantly alter the relationship between HGC and higher requirement for PICU care[45]. The hyperglycemic crisis was likely driven by infection and stress with heightened overall insulin resistance.

Iughetti et al.[46] analyzed why patients with T1DM were poorly represented between the subjects hospitalized for Covid-19 and why the cases of DKA were fewer and more severe compared with the past years. Furthermore, literature has shown how patients of all ages with T1DM did not experience a deterioration in their glucose control throughout the lockdown. Among other causes, they hypothesized was due to the surging use of telemedicine. Finally, they tried to understand how the coronavirus tropism for endocrine tissues could influence the future epidemiology of T1DM, focusing on the effects they have on pancreatic β-cells. Looking at previous research on coronaviruses, it has been demonstrated that SARS-CoV-1 binds the ACE2 receptor in the pancreatic islets. The binding between the viruses and the receptors provokes damage to the islet cells leading to acute diabetes. This happens also for SARS-CoV-2.

It is known that pancreatic β-cells are permissive to SARS-CoV-2 infection through the expression of ACE2 and that the infection may also induce indirect β-cell damage through a cytokine storm and a proinflammatory milieu. It has also been shown that inflammatory and immunological alterations following a Covid-19 infection may lead to acute and long-term disruption of glucose metabolism. A recent study showed that the combination of augmented circulating inflammatory factors that exert toxic effects on human pancreatic islet cells and SARS-CoV-2–specific viral RNA in pancreatic tissues, together with the alteration of secretory granules, promotes glucose metabolism alterations[47]. An increase in pediatric DKA admissions began one month after school closures. Given that behavioral changes started near school closure dates and viral activity peaked weeks after, this suggests that behavioral factors may not be the primary etiology and it is possible that SARS-CoV-2 infection may have direct effects on beta cells resulting in pediatric

DKA. Viral infections have been shown to precipitate development of T1DM in previously healthy children. SARS-CoV-2 enters cells via the ACE2 receptor, which is abundant in the pancreas, leading to speculation that it may contribute to T1DM pathogenesis[48] via direct cellular attack.

Margolis, et al.[49] sought to find clinical and immunological signatures of the SARS-CoV-2 virus and the Covid-19 pandemic on children newly diagnosed with T1DM. A single-center, retrospective, observational study comparing the clinical and immunological characteristics of children diagnosed with T1DM the year before and during the first 2 years of the pandemic, was performed. Data extracted from the medical records included clinical and demographic parameters, Covid-19 PCR results and the presence of anti-islet, thyroid, and celiac-related antibodies. Also obtained from the medical records was a family history of T1DM, celiac disease and autoimmune thyroid disease in first-degree family members. A total of 378 children were diagnosed with T1DM during the study period, a total of 132 in the pre-Covid era and 246 in the first 2 years of the pandemic. At diagnosis, the pH in children with DKA was lower, and HbA1C tended to be higher in the Covid-19 group compared to the pre-Covid-19 group; "7.30 [7.18, 7.35] vs 7.33 [7.19, 7.36], p = 0.046" and "110.9 mmol/mol [86.9, 129.5] or 12.65% vs 100 mmol/mol [80.3, 129.5] or 11.65%, p = 0.067]", respectively. Multiple islet antibodies (IA) were significantly more common among patients in the pre-Covid-19 group compared to the Covid-19 group "72% vs 61%, p = 0.032". Tissue transglutaminase antibodies were more common among children diagnosed in the Covid-19 compared to the pre-Covid group (16.6% vs 7.9%, p = 0.022). Their findings suggest that SARS-CoV-2 and the environmental alterations caused by the pandemic affected the clinical characteristics and the immunological profile of children diagnosed with T1DM. It is, therefore, plausible that the virus plays a more direct role in the process causing T1DM yet also plays a role in promoting generalized autoimmunity.

In a report from Germany, Kamrath, et al.[50] found that the local severity of the pandemic rather than health policy measures along with the delayed use of health care during the pandemic, appeared to be the main reason for the increase in DKA. Furthermore, the incidence of severe DKA was also higher during the Covid-19 pandemic "$p < 0.0001$" and higher among children with new onset T1DM "$p < 0.0001$". HbA1C levels, duration of insulin infusion, and length of PICU stay were significantly higher and longer during the pandemic period[51]. In general, the pandemic itself (all cause) was associated with severity of DKA as described by several groups across the world.

Treatment of DKA in Nontraditional Settings:

In the review by Agarwal, et. al[38], they note that use of subcutaneous insulin instead of intravenous (IV) insulin for management of mild-moderate DKA in a non-ICU setting worked as an effective adaptation in the face of constrained resources during the pandemic. The ISPAD Clinical Practice Consensus Guideline 2018 for management of DKA and the hyperglycemic hyperosmolar state, provide comprehensive guidance for management of DKA in young people. IV infusion of insulin remains the treatment of choice for treating DKA; however, the policy of many hospitals around the world requires admission to an ICU for IV insulin infusion. During the pandemic or other settings where intensive care resources are limited, ICU services may need to be prioritized or may not be appropriate due to risk of transmission of infection to young people with T1DM or T2DM. The aim of the guideline, which should be used in conjunction with the ISPAD 2018 guidelines, is to ensure that young individuals with DKA receive management according to best evidence in the context of limited ICU resources. Specifically, this guideline summarizes evidence for the role of subcutaneous insulin in treatment of uncomplicated mild to moderate DKA in young people and may be implemented if administration of IV insulin is not an option[52]. The pandemic forced the broader use of these guidelines to find new ways to treat DKA in a resource limited environment.

Future Directions:

The Covid-19 pandemic heavily affected health worldwide, with the various forms of diabetes in children experiencing changes at various levels, including epidemiology, diabetic ketoacidosis rates, and medical care. Some children with existing T1DM and T2DM did not show a worsening in metabolic control during the first lockdown, possibly owing to a more controlled diet by their parents. Glucose sensor and hybrid closed loop pump technology proved to be effective in all patients with T1DM during the pandemic, especially because the downloading of data allowed for the practice of tele-medicine. Telemedicine has in fact grown around the world and National Health Systems have started to consider it as a routine activity in clinical practice. The review by Zucchini, et al.[53] encompasses all these aspects related to the effects of the pandemic on the different forms of diabetes in children and how it changed the clinical management with relation to increased use of virtual surveillance and use of telemedicine that has ensued after the pandemic.

T1DM requires a holistic approach and continuous care. The Covid-19 pandemic made health care professionals realize its challenges even more ardently than in normal times. In a country like India with its huge population burden and a significant number of people with T1DM, the risk of Covid-19 in people with T1DM was considerably high. Jethwani, et al.[54] classified the challenges into three broad categories based on diabetes self-management, healthcare system effects and psychosocial aspects. They tried to provide precise, comprehensive, and region-specific solutions to these challenges. The solutions briefly included maintaining the supply chain of essentials like insulin, syringes, and glucose meter strips to increased psychological support, and financial aid/support for hospitalization in case of Covid-19 infection itself or diabetes complications including DKA. This report emphasizes that in large infectious outbreaks we need to be more aware and cognizant of attention to supportive care to prevent decompensation of children with chronic diseases. Clearly further work is needed in all of these areas.

Conclusion:

This overview provides evidence that there was a rise in pediatric DKA during and after the Covid-19 pandemic which should provide pediatric primary care providers a heightened awareness to screen for diabetes during routine care visits and watch for impending DKA in children with known T1DM that can kill or cause grave comorbid conditions. A common theme was delay in seeking medical intervention due to lockdown conditions and there was likely a direct effect of Covid-19 infection on beta cell function and dysfunction. Although much of the focus was on adult diabetes during the pandemic period and its destruction, we see here that it had a grave outcome on children with existing diabetes and brought on new cases of diabetes as well. Let us make this an example of what future outbreaks can do to children with and without diabetes and act proactively (immunize and support) to prevent the devastation on them.

References:

1. COVID-19 and Diabetes: The Tale of Two Pandemics; Elizabeth Littlejohn, MD, MS and Rebecca Schein, MD; Pediatric Annals; Volume 53Issue 7Jul 2024 : July 1, 2024 | pp.e242–e243; https://doi.org/10.3928/19382359-20240502-01.
2. Rahmati M, Yon DK, Lee SW, et al. New-onset type 1 diabetes in children and adolescents as post acute sequelae of SARS-CoV-2 infection: A systematic review and meta-analysis of cohort studies. *J Med Virol*. 2023;95(6):e28833. doi:10.1002/jmv.28833.
3. Chao LC, Vidmar AP, Georgia S. Spike in Diabetic Ketoacidosis Rates in Pediatric Type 2 Diabetes During the COVID-19 Pandemic [published correction appears in Diabetes Care. 2021 Dec;44(12):2812. doi: 10.2337/dc21-er12]. *Diabetes Care*. 2021;44(6):1451-1453. doi:10.2337/dc20-2733.
4. Jalilova A, Ata A, Demir G, et al. The Effect of the SARS-CoV-2 Pandemic on Presentation with Diabetic Ketoacidosis in Children with New Onset Type 1 Diabetes Mellitus. *J Clin Res Pediatr Endocrinol*. 2023;15(3):264-267. doi:10.4274/jcrpe.galenos.2023.2022-11-4.
5. Ho J, Rosolowsky E, Pacaud D, Huang C, Lemay JA, Brockman N, Rath M, Doulla M. Diabetic ketoacidosis at type 1 diabetes diagnosis in children during the COVID-19 pandemic. Pediatr Diabetes. 2021 Jun;22(4):552-557. doi: 10.1111/pedi.13205. Epub 2021 Mar 27. PMID: 33745226; PMCID: PMC8251027.
6. Elgenidy A, Awad AK, Saad K, et al. Incidence of diabetic ketoacidosis during COVID-19 pandemic: a meta-analysis of 124,597 children with diabetes. *Pediatr Res*. 2023;93(5):1149-1160. doi:10.1038/s41390-022-02241-2.
7. Cherubini V, Marino M, Scaramuzza AE, et al. The Silent Epidemic of Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes in Children and Adolescents in Italy During the COVID-19 Pandemic in 2020 [published correction appears in Front Endocrinol (Lausanne). 2022 Aug 04;13:977211. doi: 10.3389/fendo.2022.977211]. *Front Endocrinol (Lausanne)*. 2022;13:878634. Published 2022 Jun 17. doi:10.3389/fendo.2022.878634.
8. Qeadan F, Tingey B, Egbert J, et al. The associations between COVID-19 diagnosis, type 1 diabetes, and the risk of diabetic ketoacidosis: A nationwide cohort from the US using the Cerner Real-World Data. *PLoS One*. 2022;17(4):e0266809. Published 2022 Apr 19. doi:10.1371/journal.pone.0266809.
9. Lavik AR, Ebekozien O, Noor N, Alonso GT, Polsky S, Blackman SM, Chen J, Corathers SD, Demeterco-Berggren C, Gallagher MP, Greenfield M, Garrity A, Rompicherla S, Rapaport R, Yayah Jones NH. Trends in Type 1 Diabetic Ketoacidosis During COVID-19 Surges at 7 US Centers: Highest Burden on non-Hispanic Black Patients. J Clin Endocrinol Metab. 2022 Jun 16;107(7):1948-1955. doi: 10.1210/clinem/dgac158. PMID: 35380700; PMCID: PMC8992309.
10. Lawrence C, Seckold R, Smart C, et al. Increased paediatric presentations of severe diabetic ketoacidosis in an Australian tertiary center during the COVID-19 pandemic. *Diabet Med*. 2021;38(1):e14417. doi:10.1111/dme.14417.
11. Abdou M, Hassan MM, Hassanein SA, Elsebaie EH, Shamma RA. Presentations, Complications, and Challenges Encountered During Management of Type 1 Diabetes in Egyptian Children During COVID-19 Pandemic: A Single-Center Experience. *Front Endocrinol (Lausanne)*. 2022;13:814991. Published 2022 Mar 11. doi:10.3389/fendo.2022.814991.
12. Donbaloğlu Z, Tuhan H, Tural Kara T, et al. The Examination of the Relationship Between COVID-19 and New-Onset Type 1 Diabetes Mellitus in Children. *Turk Arch Pediatr*. 2022;57(2):222-227. doi:10.5152/TurkArchPediatr.2022.21284.
13. Chambers MA, Mecham C, Arreola EV, Sinha M. Increase in the Number of Pediatric New-Onset Diabetes and Diabetic Ketoacidosis Cases During the COVID-19 Pandemic. *Endocr Pract*. 2022;28(5):479-485. doi:10.1016/j.eprac.2022.02.005.
14. Ebekozien O, Agarwal S, Noor N, et al. Inequities in Diabetic Ketoacidosis Among Patients With Type 1 Diabetes and COVID-19: Data From 52 US Clinical Centers. *J Clin Endocrinol Metab*. 2021;106(4):e1755-e1762. doi:10.1210/clinem/dgaa920.
15. Nagl K, Waldhör T, Hofer SE, et al. Alarming Increase of Ketoacidosis Prevalence at Type 1 Diabetes-Onset in Austria-Results From a Nationwide Registry. *Front Pediatr*. 2022;10:820156. Published 2022 Feb 14. doi:10.3389/fped.2022.820156.
16. Alaqeel A, Aljuraibah F, Alsuhaibani M, et al. The Impact of COVID-19 Pandemic Lockdown on the Incidence of New-Onset Type 1 Diabetes and Ketoacidosis Among Saudi Children. *Front Endocrinol (Lausanne)*. 2021;12:669302. Published 2021 Apr 1. doi:10.3389/fendo.2021.669302.
17. Salmi H, Heinonen S, Hästbacka J, et al. New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic. *Arch Dis Child*. 2022;107(2):180-185. doi:10.1136/archdischild-2020-321220.
18. Lee YL, Nasir FFWA, Selveindran NM, Zaini AA, Lim PG, Jalaludin MY. Paediatric new onset type 1 diabetes and diabetic ketoacidosis during the COVID-19 pandemic in Malaysia. *Diabetes Res Clin Pract*. 2023;205:110981. doi:10.1016/j.diabres.2023.110981.
19. Elbarbary NS, Dos Santos TJ, de Beaufort C, Agwu JC, Calliari LE, Scaramuzza AE. COVID-19 outbreak and pediatric diabetes: Perceptions of health care professionals worldwide. *Pediatr Diabetes*. 2020;21(7):1083-1092. doi:10.1111/pedi.13084.
20. Goldman S, Pinhas-Hamiel O, Weinberg A, et al. Alarming increase in ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the first wave of the COVID-19 pandemic in Israel. *Pediatr Diabetes*. 2022;23(1):10-18. doi:10.1111/pedi.13296.
21. Leiva-Gea I, Fernández CA, Cardona-Hernandez R, et al. Increased Presentation of Diabetic Ketoacidosis and Changes in Age and Month of Type 1 Diabetes at Onset during the COVID-19 Pandemic in Spain. *J Clin Med*. 2022;11(15):4338. Published 2022 Jul 26. doi:10.3390/jcm11154338.

22. Vorgučin I, Savin M, Stanković Đ, et al. Incidence of Type 1 Diabetes Mellitus and Characteristics of Diabetic Ketoacidosis in Children and Adolescents during the First Two Years of the COVID-19 Pandemic in Vojvodina. *Medicina (Kaunas)*. 2022;58(8):1013. Published 2022 Jul 28. doi:10.3390/medicina58081013.
23. Fisler G, Izard SM, Shah S, Lewis D, Kainth MK, Hagmann SHF, Belfer JA, Feld LM, Mastroianni F, Kvasnovsky CL, Capone CA, Schneider J, Sweberg T, Schleien C, Taylor MD; Northwell COVID-19 Research Consortium. Characteristics and risk factors associated with critical illness in pediatric COVID-19. Ann Intensive Care. 2020 Dec 19;10(1):171. doi: 10.1186/s13613-020-00790-5. PMID: 33340348; PMCID: PMC7749393.
24. Parappil P, Ghimire S, Saxena A, et al. New-onset diabetic ketoacidosis with purpura fulminans in a child with COVID-19-related multisystem inflammatory syndrome. *Infect Dis (Lond)*. 2022;54(7):522-528. doi:10.1080/23744235.2022.2050423.
25. Amaral LB, Carlesse F, Rossato L. Pediatric mucormycosis associated with COVID-19: A systematic review of clinical cases. *Enferm Infecc Microbiol Clin (Engl Ed)*. 2024;42(6):321-326. doi:10.1016/j.eimce.2023.11.006.
26. Kostopoulou E. The Interplay Between COVID-19 and Pediatric Endocrine Disorders. What have we Learned After More than Three Years of the Pandemic? *Horm Metab Res*. 2024;56(3):181-192. doi:10.1055/a-2152-4590.
27. Varol F, Ozyilmaz LGB, Sahin EG, Can YY, Altas U, Cam H. Does the severity of diabetic ketoacidosis in children with type 1 diabetes change during the COVID-19 pandemic? A single-center experience from a pediatric intensive care unit. *North Clin Istanb*. 2022;9(5):429-435. Published 2022 Oct 20. doi:10.14744/nci.2022.09634.
28. Shimony H, Miller L, Reich P, et al. Pediatric diabetes mellitus hospitalizations and COVID-19 pandemic response measures. *Diabetes Res Clin Pract*. 2024;207:111060. doi:10.1016/j.diabres.2023.111060.
29. Howard MB, Basu S, Sherwin E, Cohen JS. Triple threat: new presentation with diabetic ketoacidosis, COVID-19, and cardiac arrhythmias. *Am J Emerg Med*. 2021;49:437.e5-437.e8. doi:10.1016/j.ajem.2021.04.045
30. Duong-Quy S, Huynh-Truong-Anh D, Le-Thi-Hong N, et al. Acute Respiratory Distress Syndrome Associated with Multisystem Inflammatory Syndrome in a Child with Covid-19 and Diabetic Ketoacidosis: A Case Report. *Pulm Ther*. 2022;8(3):333-342. doi:10.1007/s41030-022-00192-x.
31. Vasconez WA, Bustamante Escobar CL, Agarwal N, Solano JP, Sanchez JE. Severe Diabetic Ketoacidosis in a Child with Type-1 Diabetes, Asthma, and COVID-19. *J Pediatr Intensive Care*. 2021;10(3):232-234. doi:10.1055/s-0040-1713164.
32. Tseng YS, Tilford B, Sethuraman U, Cashen K. Combined Hyperglycemic Hyperosmolar Syndrome and Diabetic Ketoacidosis Associated with COVID-19 in a Pediatric Patient. Case Rep Crit Care. 2021 Nov 27;2021:6429710. doi: 10.1155/2021/6429710. PMID: 38442727; PMCID: PMC8627355.
33. Alizadeh, Faraz & O'Halloran, Amanda & Alghamdi, Areej & Chen, Charlotte & Trissal, Maria & Traum, Avram & Decourcey, Danielle. (2020). Toddler With New Onset Diabetes and Atypical Hemolytic Uremic Syndrome in the Setting of COVID-19. Pediatrics. 147. 10.1542/peds.2020-016774.
34. Azova S, Liu E, Wolfsdorf J. Increased Use of Hyperosmolar Therapy for Suspected Clinically Apparent Brain Injury in Pediatric Patients with Diabetic Ketoacidosis during the Peak of the COVID-19 Pandemic. *Pediatr Diabetes*. 2023;2023:5123197. doi:10.1155/2023/5123197.
35. Agathis NT, Womack LS, Webber BJ, et al. Children, adolescents, and young adults hospitalized with COVID-19 and diabetes in summer 2021. *Pediatr Diabetes*. 2022;23(7):961-967. doi:10.1111/pedi.13396.
36. Liu X, Yu Q, Li L, Wei S, Zeng J, Jiang J. Acute pancreatitis associated with diabetic ketoacidosis in a child with COVID-19 infection. *BMC Infect Dis*. 2023;23(1):381. doi:10.1186/s12879-023-08371-0.
37. Mohammad Ashraf H, Sunderajan T, Pierre L, Kondamudi N, Adeyinka A. Aversion to Hospital Admission Due to Fear of COVID Infection Leading to Fatality From Diabetic Ketoacidosis. *Cureus*. 2021;13(12):e20251; doi:10.7759/cureus.20251.
38. Agarwal A, Bansal D, Nallasamy K, Jayashree M, William V. Pediatric Diabetes and Diabetic Ketoacidosis After COVID-19: Challenges Faced and Lessons Learnt. Pediatric Health Med Ther. 2023 Sep 4;14:281-288. doi: 10.2147/PHMT.S384104. PMID: 37691882; PMCID: PMC10488656.
39. Foster T, Haller M, Atkinson M, Schatz D; Delayed diagnosis of diabetic ketoacidosis and associated mortality during the COVID-19 pandemic; Journal of Diabetes. 2021 Jun; 10; 837-839; doi.org/10.1111/1753-0407.13208.
40. Modarelli R, Balikcioglu PG, Hendrix G, DeRusso M, Ozment C. The Perfect Storm: Rapid Progression of Diabetic Ketoacidosis in Pediatric Diabetes in the Setting of COVID-19. *AACE Clin Case Rep*. 2021;7(6):357-359. doi:10.1016/j.aace.2021.05.007.
41. Dżygało K, Nowaczyk J, Szwilling A, Kowalska A. Increased frequency of severe diabetic ketoacidosis at type 1 diabetes onset among children during COVID-19 pandemic lockdown: an observational cohort study. Zwiększona częstość występowania ciężkiej cukrzycowej kwasicy ketonowej u dzieci z cukrzycą typu 1 w czasie pandemii COVID-19: kohortowe badanie obserwacyjne. *Pediatr Endocrinol Diabetes Metab*. 2020;26(4):167-175. doi:10.5114/pedm.2020.101003.
42. Alaqeel A, Aljuraibah F, Alsuhaibani M, et al. The Impact of COVID-19 Pandemic Lockdown on the Incidence of New-Onset Type 1 Diabetes and Ketoacidosis Among Saudi Children. *Front Endocrinol (Lausanne)*. 2021;12:669302. Published 2021 Apr 1. doi:10.3389/fendo.2021.669302.
43. Wu Z, Wang J, Ullah R, et al. Covid 19 and diabetes in children: advances and strategies. *Diabetol Metab Syndr*. 2024;16(1):28. Published 2024 Jan 29. doi:10.1186/s13098-024-01267-2.

44. Keiner ES, Slaughter JC, Datye KA, Cherrington AD, Moore DJ, Gregory JM. COVID-19 Exacerbates Insulin Resistance During Diabetic Ketoacidosis in Pediatric Patients With Type 1 Diabetes. *Diabetes Care*. 2022;45(10):2406-2411. doi:10.2337/dc22-0396.
45. Toomey V, Klein MJ, Vidmar AP, Chao LC, Pineda J, Bhalla A. Association Between COVID-19 and Severity of Illness for Children With Hyperglycemic Crisis. *Hosp Pediatr*. 2023;13(9):794-801. doi:10.1542/hpeds.2023-007195.
46. Iughetti L, Trevisani V, Cattini U, et al. COVID-19 and Type 1 Diabetes: Concerns and Challenges. *Acta Biomed*. 2020;91(3):e2020033. Published 2020 Sep 7. doi:10.23750/abm.v91i3.10366.
47. Montefusco L, Pastore I, Lunati ME, Fiorina P. Increased Risk of Diabetes and Diabetic Ketoacidosis Associated With COVID-19. *Diabetes*. 2023;72(5):560-561. doi:10.2337/db22-0908.
48. McCluskey CK, Zee-Cheng JE, Klein MJ, et al. The Temporal Relationship Between Local School Closure and Increased Incidence of Pediatric Diabetic Ketoacidosis. *Front Pediatr*. 2022;10:812265. Published 2022 Mar 11. doi:10.3389/fped.2022.812265.
49. Margolis MG, Weizman S, Lazar L, et al. Clinical and immunological characteristics of children diagnosed with-Type 1 diabetes during the COVID-19 pandemic. *Diabet Med*. 2024;41(5):e15250. doi:10.1111/dme.15250.
50. Kamrath C, Rosenbauer J, Eckert AJ, et al. Incidence of COVID-19 and Risk of Diabetic Ketoacidosis in New-Onset Type 1 Diabetes. *Pediatrics*. 2021;148(3):e2021050856. doi:10.1542/peds.2021-050856.
51. Kiral E, Kirel B, Havan M, Keskin M, Karaoglan M, Yildirim A, Kangin M, Talay MN, Urun T, Altug U, Kesici S, Tufan E, Kacmaz E, Bozan G, Azapagasi E, Uysal Yazici M, Ozturk Z, Yesilbas O, Karaguzel G, Kaya G, Barlas U, Duyu M, Boyraz M, Sevketoglu E, Akcay N, Hancili S, Guven A, Dursun O, Ulgen Tekerek N, Ozcifci G, Yazici P, Turanli E, Kendirli T, Kahveci F, Yetimakman AF, Citak A, Şik G, Bingol I, Aygun F, Durak C, Yilmaz R, Bugrul F, Sari Y, Tekguç H, Albayrak H, Yener N, Agin H, Soydan E, Yildizdas D, Dilek SO, Yalindag N, Incekoy-Girgin F, Alacakir N, Tutunculer F, Arslanaoglu MO, Aydin C, Bilgin M, Simsek E, Dinleyici EC. Increased Severe Cases and New-Onset Type 1 Diabetes Among Children Presenting With Diabetic Ketoacidosis During First Year of COVID-19 Pandemic in Turkey. Front Pediatr. 2022 Jun 29;10:926013. doi: 10.3389/fped.2022.926013. PMID: 35844756; PMCID: PMC9277100.
52. Priyambada L, Wolfsdorf JI, Brink SJ, et al. ISPAD Clinical Practice Consensus Guideline: Diabetic ketoacidosis in the time of COVID-19 and resource-limited settings-role of subcutaneous insulin. *Pediatr Diabetes*. 2020;21(8):1394-1402. doi:10.1111/pedi.13118.
53. Zucchini S, Scozzarella A, Maltoni G. Multiple influences of the COVID-19 pandemic on children with diabetes: Changes in epidemiology, metabolic control and medical care. World J Diabetes. 2023 Mar 15;14(3):198-208. doi: 10.4239/wjd.v14.i3.198. PMID: 37035223; PMCID: PMC10075036.
54. Jethwani P, Saboo B, Jethwani L, Kesavadev J, Kalra S, Sahay R, Agarwal S, Hasnani D. Management of children and adolescents having type 1 diabetes during COVID-19 pandemic in India: challenges and solutions. Int J Diabetes Dev Ctries. 2020 Sep;40(3):335-339. doi: 10.1007/s13410-020-00865-w. Epub 2020 Sep 15. PMID: 32952333; PMCID: PMC7490475.

