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Clinical profile and outcome of children with Type 1 Diabetes Mellitus presenting with Diabetic Ketoacidosis in the COVID- 19 pandemic

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Abstract

Background: The potential pathogenic links between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and incidence of diabetes mellitus (DM) as well as increased severity of illness with COVID-19 in the adult diabetic population has been well documented (1). With dearth of pediatric data in India on the links between COVID-19 and new onset DM, our study highlights the characteristics and outcomes of children who presented in diabetic ketoacidosis (DKA) during the pandemic and compares those who had COVID-19 to those who did not. All children admitted to the PICU in DKA during the COVID-19 pandemic from June 2020 to August 2022 were included. Their clinical data and laboratory investigations and outcomes were analysed using SPSS software. 48 children were included. 7 tested positive for SARS-CoV-2 by RT-PCR. 32 were newly diagnosed patients, 6 of whom were COVID positive and 16 previously diagnosed with 1 being COVID positive. Mean age group for COVID positive was 11.32 and COVID negative was 9.68. Severity of acidosis was more in the COVID negative group. Statistically significant differences were noted in serum sodium levels, mean pH levels, bicarbonate levels, HbA1c levels, total leucocyte counts between the 2 groups. Mean duration of correction of acidosis was 24.4 hours in COVID positive patients and 28.4 in COVID negative patients. No mortality in either group was noted. The increased incidence of new onset type I DM during the pandemic with several children testing positive for COVID-19 highlights the potential pathogenic link between the two entities.

Key words: SARS-CoV-2, Pandemic, Incidence, Diabetic Ketoacidosis, Diabetes Mellitus, Type 1.

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Introduction

Numerous pieces of evidence about the novel coronavirus COVID-19's connection to type 2 diabetes surfaced after the WHO declared it to be a worldwide pandemic on March 11, 2020. However, the information on how SARS-CoV-2 infection affects people with T1DM is relatively recent and scant. The knowledge gained from previous coronavirus outbreaks

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(SARS and MERS) implies that islet cell damage brought on by coronaviruses is not a recent occurrence(2). Any concurrent illness, such as pneumonia and other urinary tract infections, can cause ketoacidosis, which is a pro-inflammatory state on its own(3). The functional receptor for SARS-CoV-1 and -2 was discovered to be ACE2, a new homolog of ACE that degrades angiotensin-II and angiotensin-I-VII. SARS Cov can bind to ACE2 expressed on the pancreatic islet cells, inducing cell death and extreme insulinopenia(2). Theoretically, the pro-inflammatory condition present in even mildly affected COVID 19 patients can encourage ketogenesis, triggering DKA(4). There is lack of literature regarding paediatric patients with COVID 19 and DKA.

Early on in the pandemic, there were 23% newer instances of childhood diabetes reported annually in Italy, yet those who did present had more severe DKA in 2020 than in 2019 (44.3% vs. 36%). Germany reported a two-fold rise in DKA and severe ketoacidosis at the time of diabetes diagnosis in children and adolescents during the COVID-19 pandemic, while the UK recorded an increase in the referral of kids with DKA compared to prior years(5–7).

A recent big data analysis from the United States observed that the individuals aged <18 years with COVID-19 were more likely to be newly diagnosed with diabetes in >30 days after infection than those without COVID-19 and those with non–SARS-CoV-2 respiratory infections(8,9).

Whether this new-onset diabetes is a traditional T1DM or a different type of diabetes itself remains a mystery. It is also unknown whether the severe COVID-19-induced hyperglycaemia observed in some people would go away over time like the diabetes caused by SARS-CoV-1. It is impossible to predict how COVID-19 alters the course of the disease in those with pre-existing diabetes(10).

Methodology

This was a prospective, observational and analytical study done in a tertiary hospital in Pune, Maharashtra. 48 patients (24 males,24 females) were included in the study which was conducted over a period of 2 years. According to the International Society for Pediatric and Adolescent Diabetes (ISPAD) 2018 recommendations, DKA was diagnosed in patients who had hyperglycaemia (blood glucose > 11 mmol/L), moderate or large urine ketones, and acidosis (venous pH <7.3 or serum bicarbonate <15mmol/L). Depending on the severity, they were subsequently admitted to our unit's PICU or step-down PICU, where treatment was started. They were classified into mild moderate and severe based on the biochemical parameters as mentioned in the ISPAD protocol which are mentioned below

1. Mild: venous pH<7.3 or serum bicarbonate <15 mmol/L
2. Moderate: pH <7.2, serum bicarbonate <10 mmol/L
3. Severe: pH <7.1, serum bicarbonate <5 mmol/L.

The fluid strategy management recommendations according to ISPAD protocol, were used to treat DKA in all of the patients. To determine the time required to reverse acidosis and close the anion gap, the biochemical parameters were examined. The ABGs were recorded every six hourly and using repeated measures of Anova and Bonferoni pairwise comparisons, all variables were compared as within subject factors. Statistical analysis was done using SPSS software version 25.

Based on the criteria outlined in the ISPAD protocol, the diagnosis of DKA was verified in all 48 patients and were subsequently given 0.9 percent normal saline fluid boluses according to their level of hydration with repeat fluid boluses as required with a maximum dose of 20ml/kg for severe DKA at the first hour.

After priming the insulin, all patients received insulin replacement at a rate of 0.1units/kg/hour. For insulin therapy, regular short-acting insulin (Human Actrapid - NovoNordisk) was administered. After the fluid bolus, maintenance fluids for 48 hours were

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determined and begun. Only after recording the urine output was potassium replacement (10mEq/500ml) added to the maintenance fluids given following the bolus. According to the degree of dehydration, the fluid deficit was computed as 5% (50ml/kg), 7% (70ml/kg), and 10% (100ml/kg) and included in the maintenance fluids. After the bolus and the initiation of maintenance fluids insulin was administered. Throughout the correction period, vital signs, GCS, input, and output were continuously monitored.

Fluids containing 5 percent dextrose (0.45% DNS) were added when blood sugar levels fell below 250 mg/dl, and fluids containing 10 percent dextrose were added when they fell below 150 mg/dl. Replacement of urine losses exceeding 4 ml/kg/hour was done if the child became polyuric as a result of increased renal perfusion. After six hours of treatment, 0.45 percent DNS was often administered to prevent the onset of hyperchloremic acidosis. Throughout the period the serum sodium levels, corrected sodium levels, serum potassium levels, serum chloride levels were monitored every 6 hourly along with the ABG. In addition to the potassium in the IV fluids, potassium replacement was done. Hyponatremia known to be associated with high blood glucose levels was noted initially and increase in serum sodium levels (0.5 mmol for each 1 mmol) with the initiation of therapy and reduction of blood sugar levels was monitored. If hyperchloremic acidosis was noted then the fluids were switched over from 0.9 percent DNS to 0.45 percent DNS. Insulin was continued until there was resolution of DKA which was taken as pH>7.3, serum bicarbonate >15 mmol, closure of the anion gap as per ISPAD protocol. Blood beta hydroxy butyrate levels could not be measured.

Results

The study included 48 pediatric patients who presented with DKA of which 7 tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by RT-PCR. There were 32 newly diagnosed patients with DKA, 6 of whom were COVID positive and 16 previously diagnosed patients with DKA with 1 patient being COVID positive. Mean age group for COVID positive was 11.29 years and non-COVID positive patients was 9.78 years. Male gender predominant DKA was noted in both COVID positive and non-positive groups. Both groups had similar presenting symptoms with nausea being more statistically significant in the COVID positive group. Based on biochemical parameters the COVID positive group had values ranging from mild to moderate DKA compared to the non-COVID positive group whose values were along the range of severe DKA. Statistically significant differences (p value < 0.005) were noted in serum sodium levels, mean pH levels, bicarbonate levels and HbA1c levels (Table I). In COVID positive patients, mean pH at zero hours was 7.21 and at 36 hours was 7.29, mean bicarbonate levels were 13.6 at 6 hours and 16.43 at 12 hours and initial mean serum sodium levels were 140.33. In non-COVID positive patients mean pH at zero hours was 7.07 and at 36 hours was 7.39, mean bicarbonate levels were 8.8 at 6 hours and 12.9 at 12 hours and initial mean serum sodium levels were 135. Differences were also noted among HbA1c levels with a mean of 10.8 in COVID positive patients and 13.8 in non-COVID positive patients. Mortality from COVID-19 in our study was 0%. Mean duration of correction of acidosis was 24.4 hours in COVID positive patients and 28.4 in non-COVID positive patients. Both groups were treated for DKA according to ISPAD protocol. No additional antiviral therapy like remdesivir was required for the COVID positive patients. Comparison of TLC counts in COVID versus non COVID was also statistically significant with mean TLC of 12,285.71 in COVID positive and 20,757.35 in non-COVID positive patients with no significant differences in the differential counts.

Discussion

SARS-CoV-2 binds to Angiotensin-converting enzyme 2 (ACE2) by a complex mechanism which causes endocytosis of the virus complex(2,11), which may directly aggravate beta cell

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injury(12) and increased angiotensin II can impede insulin secretion(13). The onset of the pandemic saw a rise in the number of patients with diabetes mellitus(14)mainly due to the unintentional neglect of non-essential care during the pandemic. Exposure to seasonal viruses had reduced due to decreased social interactions (school closures and quarantine) and relatively better hygiene precautions during the pandemic, hence the possibility that new onset DM in children could be triggered by SARS-CoV-2 pandemic which was the most prevalent diabetogenic virus in this period is not far off.

In our study all the COVID positive patients had presented with mild to moderate DKA as compared to the non COVID positive patients who had presented with severe DKA which had come as statistically significant (p value <0.005). This could be because most of the COVID positive patients were newly diagnosed whereas the non-positive group had chronic patients along with new cases. There could also be delayed presentation to the hospital and the underlying causes of this occurrence may be complex and include lack of access to primary care services, parental reluctance to seek care during the pandemic, and a delay in T1DM diagnosis in newly diagnosed patients(5–7).

Similarly, comparison of the sodium levels showed near normal initial sodium levels in COVID positive patients as compared to non-positive patients who had come with hyponatremia which correlated as they had severe DKA at presentation. There was no additional treatment required for the COVID positive patients and no mortality was noted in either group. The average total leucocyte count was raised in the non-positive patients who had severe acidosis. Almost 6 patients had new onset diabetes precipitated by COVID 19.

It is already known in adults that patients with pre-existing diabetes are prone for secondary infections and rapid deterioration requiring prolonged hospital stay especially when COVID positive(1). The COVID positive patients in our study did not develop any secondary infections during the course of their stay and the time taken to recover was almost the same as the non-positive patients. There was no statistically significant difference in the time required for correction of DKA.

The glycaemic variability seen with the onset of the COVID 19 is one of the reasons for the stress hyperglycaemic response going above the values expected in severe infections and resulting in essentially a type of ketosis prone diabetes. The altered glucose metabolism led to increased HbA1c levels in these patients. Maintaining target HbA1C levels helps to prevent complications in patients with type 1 diabetes(15) but reference ranges of HbA1C levels at which DKA gets precipitated remains unknown. It is unclear whether the phenotype of the new-onset diabetes triggered by COVID-19 is the classic type 1, or type 2, or a new type and whether its alterations of glucose metabolism are transient or persistent(16,17), On this note, DKA being the initial manifestation of COVID 19 after altering glucose metabolism over a prolonged period of time is also a point to be considered.

COVID 19, a RNA virus was prone for a number of mutations(18). The WHO had named the variants prone to cause more severe infections as “variants of concern” and with the onset of the pandemic in India(19) with the delta variant, many problems arose like diagnostic difficulties, varied symptoms, and rapid spread across the country. The unique nature of these viruses which helped them evade immunity had serious impact on already immunocompromised individuals and the need for multivalent vaccines similar to Influenza becomes essential. It is unclear whether the glycemic variability was a result of one specific mutation or whether all the mutant strains were diabetogenic and not much research is available on that point. If specific strains can be identified which are diabetogenic then specific vaccines can be manufactured and vaccine preventable diabetes can be the future.

Controversy exists over the expression of ACE2 in human pancreatic cells (20–22), and direct cell malfunction does not adequately explain the pathogenic mechanism of SARS-CoV-2 infection–induced diabetes. When compared to patients with other critical illnesses,

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insulin resistance in COVID-19 patients appears to be abnormal (23). This might have an impact on how COVID-19 develops new-onset diabetes or hyperglycaemia. Diabetes-free COVID-19 patients also showed hyperglycaemia and insulin resistance, according to Montefusco and colleagues (24). Six months after acute COVID-19 infections, hyperglycaemia (24) and insulin resistance (25) were found to be persistent. Additionally, the stomach is less focused on glucose homeostasis in patients with coronavirus infection than the pancreas, liver, skeletal muscle, and adipose tissue. Hyperglycemia in COVID-19 patients, however, may also be brought on by enhanced intestinal glucose absorption through the sodium-dependent glucose transporter (SGLT1) in the intestinal epithelium, which is mediated by the downregulation of ACE2 with a SARS-CoV-2 infection (26).

All parameters studied sequentially as within subject factors showed significant improvement in the initial few hours and the values had plateaued over time. There was no significant difference in the time required for correction of the acidosis in both groups. As most of the manifestations were mild, the possibility of viral infection triggered beta cell injury being a transient phenomenon due to less destruction cannot be disregarded.

A study in 2010 looking into the pathophysiology of pancreatic lesions discovered that while exocrine tissues are only slightly immune-positive for ACE2, pancreatic islets are substantially immune-positive. Twenty of the 39 patients (age: 47.2 ± 2.2 years) who did not receive corticosteroids during the SARS sickness developed insulin-dependent diabetes while they were hospitalised. Six of them had diabetes when they were discharged. However, just two patients remained diabetic following a 3-year follow-up, indicating that the damage to islet cells is severe and largely temporary(2) . At last follow-up, these patients had normoglycemia on oral anti-hyperglycemic medication(1,27). How COVID-19 changes the natural history of disease in those with pre-existing diabetes was difficult to(10) understand in adults.

The reduced number of cases in our study could be a limiting factor towards reaching a definitive diagnosis. Long term follow up studies are required to determine whether this diabetes mellitus is a transient phenomenon or whether the virus can linger to cause recurrence. Seasonality of the COVID 19 viruses precipitating DKA is yet to be seen. Whether usage of vaccines can serve as a preventive measure for COVID-19 and thereby diabetes itself especially in those who are genetically predisposed to DKA is also an important point to consider. Whether DKA by itself could be the initial manifestation of SARS-CoV-2 infection also needs further studies.

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