http:// ijp.mums.ac.ir
Original Article (Pages: 18449-18460)

Sars-cov-2 Infection Is a Potential Risk of Diabetic Ketoacidosis in Children Diagnosed with Type i Diabetes. An Observational Study

Noura M. Ibrahim El Bakry [1], Yossra Samir Fadle [1], Ayat Mostafa Mohamed [2], Sara Mahmoud Farhan [3], Dalia Nabil Kotb 4, * Nagwa M. Sabry Mahmoud [1]

[1] Pediatric Department, Faculty of Medicine, Minia University, Egypt.

[2] Clinical pathology department, Faculty of Medicine, Minia University, Egypt.

[3] Microbiology and immunology department, faculty of pharmacy, Deraya University, Egypt.

[4] Medical Microbiology and Immunology Department, Faculty of Medicine, Minia University, Egypt.

Abstract

Background: Since the beginning of COVID-19 pandemic, several studies have reported increased type 1 diabetes (T1D) and severe diabetic ketoacidosis (DKA) in children. Recent studies have linked viruses to T1D due to their autoimmune nature. SARS-CoV-2 infection may cause hyperglycemia and DKA. In this study we aimed to evaluate the incidence of DKA in pediatric patients with T1D during the initial COVID-19 pandemic and the years preceding it.

Methods: The present study is a retrospective observational investigation conducted at Minia University Hospital's Pediatric Intensive Care Unit (PICU). Children diagnosed with T1D who recently had SARS-CoV-2, as validated by laboratory testing with the RT-PCR method, were included in the study. The cases referred to during the period from March 2020 to February 2022, which coincided with the pandemic, were compared with those newly diagnosed with diabetes and presented with DKA from March 2018 to February 2020, the pre-pandemic phase. Comparisons were made on the incidence, frequency, and diagnostic criteria.

Results: During the pandemic period, we admitted 212 cases of new-onset T1D. Of these, 159 (75%) patients had DKA, and 53 (25%) had hyperglycemia. Comparing the pre-pandemic with the pandemic period, we noted that the number of children identified with T1D had risen from 4.99/100,000children per year in pre-pandemic periods to 8.46 /100 000 PY in the pandemic period with an incidence rate ratio (IRR) of 6.25 (95% CI 2.90 to 7.83); p<0.0001.

Conclusion: COVID-19 pandemic has caused a rise in the number of children with newly diagnosed diabetes, and more people with newly diagnosed diabetes are now presenting with severe DKA.

Key Words: COVID-19, diabetic ketoacidosis, diabetes mellitus, SARS-CoV-2.

* Please cite this article as: Ibrahim El Bakry NM, Samir Fadle Y, Mostafa Mohamed A, Mahmoud Farhan S, Nabil Kotb D, Sabry Mahmoud NM. Sars-cov-2 Infection Is a Potential Risk of Diabetic Ketoacidosis in Children Diagnosed with Type i Diabetes. An Observational Study. Int J Pediatr 2024; 12 (01):18449-18460. DOI: **10.22038/ijp.2024.76289.5394**

Corresponding Author:

Nagwa M. Sabry Mahmoud, Pediatric Department, Faculty of Medicine, Minia University, Egypt. Email: dr_nagwa163@ mu.edu.eg.

Received date: Nov.18,2023; Accepted date: Jan.17,2024

1- INTRODUCTION

SARS-CoV-2 caused an illness known as "COVID-19," and on March 11, 2020, the World Health Organization formally proclaimed the outbreak of COVID-19 pandemic and a public health emergency of worldwide significance (1). Large, positive-strand ribonucleic viruses are called coronaviruses. Human coronaviruses (HCoVs) are viruses belonging to just two genera that can infect humans: the “a” and “b” types (2). Human HCoVs are considered mild phenotypes due to their minimal pathogenic effect. However, the early 21st century saw the emergence of two epidemics with significant rates of illness and mortality: Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (3). In general, COVID-19 is more common in people over 15, with fewer verified occurrences in younger patients with milder symptoms (4).

However, with severe cases or other comorbidities or risk factors like cardiovascular diseases or diabetes, especially type 1 diabetic mellitus (T1DM), advanced consequences such as renal or circulatory failure have been recorded (5). A shortage in insulin manufacturing characterizes type 1 diabetes (T1DM), a metabolic disorder with varying effects on the body's metabolism. It is one of the most common long-term illnesses in children and has become more common in the last few years (6).

DKA frequency varies by region, with 15% occurrence in Europe and 70% in North America (7). DKA is the main acute, potentially fatal consequence associated with the development of T1DM (8). Data from the first few months of 2020 point to a reciprocal association between COVID-19 and diabetes (9). Diabetes is linked to COVID-19 severity and mortality and is consistently proposed as a risk factor for the virus (10). Multiple forms of diabetes might be observed in patients with COVID-19, including new-onset diabetes and metabolic complications such as diabetic ketoacidosis and hyperosmolarity (11). However, there is a dearth of information regarding type 1 diabetes with new start during the COVID-19 pandemic, especially in children (12).

However, a report of multicenter regional data from North West London on children with DKA and new-onset T1DM estimates that the COVID-19 pandemic caused an 80% increase in new-onset T1DM cases. The report also suggests that COVID-19 exposure may have contributed to the observed increase in cases by hastening or precipitating the onset of new-onset T1DM (12).

According to a prior study, children made up about 5% of verified COVID-19 cases and had milder disease symptoms. They also had a far lower death rate than adults and a better outlook for youngsters. However, whether their diabetes is new-onset or undiagnosed, children with recently diagnosed diabetes typically exhibit higher levels of inflammatory markers and signs of multiorgan injury that can result in a severe or catastrophic COVID-19 disease (13). Additionally, they exhibit severe hyperglycemic consequences that call for large insulin doses, such as DKA and hyperosmolar hyperglycemic syndrome (14). The death rate for COVID-19 patients with newly diagnosed diabetes is greater than that of people with known diabetes (13).

The objective of this study was to assess the occurrence, frequency, and diagnostic criteria of newly diagnosed diabetes cases in children presented with diabetic ketoacidosis (DKA) during the initial phase of the COVID-19 pandemic and to compare these findings with the period prior to the pandemic.

2- MATERIALS AND METHODS

2-1. Design and population

This study included a retrospective analysis of the medical records of 498 patients who were admitted to the hospital between March 2018 and February 2020 (the pre-pandemic period) and 906 patients diagnosed with T1D who were admitted to the PICU and endocrine unit at Minia University Hospital between March 2020 and February 2022 (during the pandemic period).

This retrospective cohort analysis included two datasets of children who were diagnosed with the new onset of Type 1 diabetes (T1D) between March 2020 and February 2022 (during the pandemic) and between March 2018 and February 2020 (during the period before the pandemic).

All children who were newly diagnosed with T1D and severe DKA and who were hospitalized in the PICU endocrine unit at Minia University Hospital in Egypt are included in the first dataset. All children admitted to the same hospital were included in the second database. Serum samples from some of the cohort's children were used for SARS-CoV-2 antibody testing throughout the pandemic.

2-2. Setting

The study was carried out in Minia City, Egypt, which has a population of 8 million at the date of December 31, 2021. The only facility in Minia City that offers a pediatric intensive care unit and advanced tertiary-level care is Minia University Hospital. Hence, the prevalence of severe DKA in this specific group can be ascertained by analyzing the number of patients treated at the university hospital in Minia. The PICU admission requirements remained unchanged throughout the pandemic. The pediatric critical care unit exclusively catered to children and did not provide medical care for adults.

2-3. Participants

This study examined the medical records of all newly diagnosed children under the age of 18 with Type 1 Diabetes (T1D) who received treatment in the Pediatric Intensive Care Unit (PICU) and Endocrine Unit at Minia University Hospital during the pandemic period (March 2020 to February 2022) and the equivalent time frame before the pandemic (March 2018 to February 2020). The pre-pandemic period, spanning from March 2018 to February 2020, had a total of 212 recordings. Compared to that, the pandemic period, from March 2020 to February 2022, had 105 records.

2-3-1. Inclusion and exclusion criteria

This study included only children who were diagnosed with T1D during the period from March 2020 to February 2022 (referred to as the pandemic period), as well as the similar period from March 2018 to February 2020 (referred to as the pre-pandemic period). All participants in the study were under the age of 18. They included children admitted to the Pediatric Intensive Care Unit (PICU) or endocrine unit with high blood glucose levels (hyperglycemia), diabetic acidosis, or ketosis, and who have been diagnosed with Type 1 Diabetes (T1D) either recently or currently, as well as children experiencing difficulty breathing and reduced oxygen levels. T1D was identified by the presence of autoantibodies, random blood glucose levels exceeding 200 mg/dL, fasting glucose levels above 126 mg/dL, and postprandial glucose levels exceeding 200 mg/dL after 2 hours (1). DKA was characterized by blood sugar levels exceeding 11 mmol/L (200 mg/dL), venous pH of 7.3 or higher, bicarbonate levels less than 15 mmol/L, presence of ketones in the blood (ketonemia), and presence of ketones in the urine (ketonuria) (10). We reviewed the number of individuals diagnosed with T1D, DKA, and COVID-19, as well as those requiring

hospitalization in the PICU. In the study, we reviewed the medical records of all patients regarding their recurrent admissions for T1D-related diabetic ketoacidosis (DKA), their adherence to insulin treatment, and the presence of respiratory symptoms such as coughing, difficulty breathing, and cyanosis. Additionally, they were reviewed for symptoms associated with infection, including fever, loss of appetite, headaches, and other related symptoms. A pulse oximetry measurement to assess O2 saturation and a chest computed tomography (C.T.) scans were done for every patient. SARS-CoV-2 was identified in children with Type 1 Diabetes using PCR. The study excluded children with T1D admitted to the (PICU) for unrelated conditions. The research was carried out under the auspices of Minia University's administration and with the approval of the faculty of medicine at Minia University.

2-4. Data Collection

This study examined patient records on analysis features and demographic data. Within this group, we evaluated arterial blood gasses, serum osmolality, and serum glucose levels. The investigation specifically assessed pH and glucose levels. We assessed the duration of symptoms before diagnosis and the HbA1C level at the time of diagnosis as potential indicators of diagnostic delay.

Utilizing a fully automated chemical auto-analyzer, Dimension-ES, USA, 7 ml of venous blood samples were taken in order to perform tests on random blood glucose (RBG), HbA1C, white blood cell count with differential, and arterial blood gasses (ABG). A coronavirus PCR was also conducted.

2-4-1. Real Time (RT) PCR for Covid 19

1-Sample Preparation Procedure: Every time an extraction is carried out, at least 1 negative extraction control (NEC) (i.e., an extraction without the addition of a sample) should be prepared. This NEC will act as the whole testing system's negative control (**Table 1**).

Table-1: Sample Preparation Procedure

Steps	Nasopharyngeal swabs
Collection	Dacron or polyester flocked swabs in a viral transit medium
Temperature during transit	4°C
Short-term holding (pre-extraction)	4°C for ≤ 5 days
Long-term storage (pre-extraction)	For extended durations, -70°C
Extraction System	CE IVD extraction apparatus designed for RNA isolation
Extraction sample volume	700 µL
Extraction elution volume	85 µL

2-RNA extraction: For being utilized in the extraction of RNA from clinical samples, such as nasopharyngeal & oropharyngeal swabs, and/or sputum, the Real-Time PCR CE IVD was created to be utilized with an extraction system recognized as a CE IVD device.

The GXT DNA/RNA Extraction kit (CE IVD) was used to extract the genome utilizing the automated extraction equipment GenoXtract® from HAIN

Lifescience GmbH (Brucker). The 1000 µl template preparation buffer was used to pause the internal extraction control. The extraction included its incorporation. Primer design recommends that 20 µl be added to each sample. Samples were mixed with a buffer; then the internal extraction control was added to the sample.

Table-2: PCR amplification

Steps	Time	Temperature	Cycles	Detection format
Reverse transcription	10 min	55°C	1	COVID-19 = FAM (465-510) Internal Extraction Control (IEC) = VIC / HEX / Yellow 555 (533-580)
Taq activation, or first denaturation	2 min	95°C	1	
Denaturation	10 sec.	95°C	45	
Annealing and Extension	60 sec	60°C *		

* Achieving acquisition was done after this phase.

COVID 19 RNA: All the data were analyzed and the criteria were fulfilled, the samples were assessed by Applied Biosystems 3730XL Sequencers: Macrogen, Korea.

2-5. Data analysis

Non-numerical data were described as percentages, whereas numerical variables were expressed as means and standard deviations. Using two-tailed t-tests, the variations between the control and patient groups were calculated. P-values below 0.05 were regarded as significant. Pearson correlation coefficient determined the magnitude of correlations. Using the statistical software Prism 3.0, all data were evaluated (Graph Pad Software, USA: San Diego, CA). Microsoft Office Excel 2016 was utilized to calculate the numbers.

3- RESULTS

This study used a retrospective analysis of medical records of children diagnosed with T1D between March 2020 and February 2022 (The pandemic period) and between March 2018 and February 2020 (the pre-pandemic period). During the Pandemic, a total of 212 children who were recently diagnosed with T1D were admitted to PICU, whereas only 105 children were admitted during the equivalent period before the Pandemic. The incidence increased from 4.99/100,000 person-years (PY) during pre-pandemic periods to 8.46/100,000 PY during the pandemic study period, with an IRR of 6.25 (95% CI: 2.9 to 7.8), p 0.0001 (**Table 3**).

Since the severity of acidosis and hyperosmolarity was consistent across all periods, the increase could not be attributed to an existing trend or a lowered admission standard (**Table 3**). Children newly diagnosed with T1D during the pandemic period (N=212) were admitted to PICU or endocrine unit; 133 (63.33%) had DKA (Group I). Out of the patients, 77 (36.67%) showed hyperglycemia without DKA (Group II). There were no significant differences in age and gender across the groups (p=0.1 and 0.2, respectively). The information is presented in **Table 4**. The arterial blood gas (ABG) profiles of bicarbonate (HCO3), carbon dioxide (CO2), and partial pressure of oxygen (PO2) showed significant differences across the groups (P=0.001*, 0.01*, and 0.001*, respectively). Significant differences were seen between groups regarding oxygen saturation and chest computed tomography (p<0.001* and p<0.02*, respectively). A statistically

significant difference was seen between the study groups (p=0.010* and 0.035*, respectively) regarding severe hyperglycemia and lymphocyte count. There was no significant difference in PH value between the groups (p=0.4). The HBA1c% did not differ significantly across the groups (p=0.4; **Table 5**).

There were 159 cases of COVID-19 patients who had DKA, accounting for 75% of the total. A total of 41 male patients (19.34%) and 26 female patients (12.26%) were diagnosed with newly-onset diabetes. Upon admission, 19 patients (8.96%) diagnosed with COVID-19 demonstrated DKA, while 13 patients (6.13%) came with hyperglycemia alone, without DKA. These diagnoses were determined based on nasopharyngeal polymerase chain reaction (PCR) testing results. Out of the total number of patients, 34 (16.03%) were diagnosed with DKA, and 3 (1.42%) were diagnosed with hyperglycemia without DKA. These patients tested positive for COVID-19 based on the presence of serum COVID antibodies (IgG and/or IgM) and were classified as post-COVID patients.

Table-3: Characters and laboratory data of the children admitted with new onset T1D during the pandemic and the pre pandemic study periods

Variable	Pre pandemic periods	Pandemic period	P value
Number of patients per study period, n (%)	N=105 (75%)	N=212 (25%)	-
Incidence, per 100 000 person-years (PY) (95% CI)	4.99 (95% CI 2.90)	8.46 (95% CI 7.83)	0.0001*
Age, median (IQR), years	8.5 (6.4–11.5)	11.0 (8.1–11.3)	0.42
Female sex, n (%)	47 (44.76)	90 (42.45)	0.6977
Male sex n (%)	58 (55.24)	122(57.54)	
Altered level of consciousness, n (%)	58(55.24)	156 (73.58)	0.73
Severe DKA (blood pH <7.10), n (%)	53 (50.48)	148 (69.81)	1.00
Laboratory values:			
pH, median (IQR)	7.05 (6.87–7.20)	7.02 (6.71–7.23)	0.47
Glucose, median (IQR), mmol/L	32.5 (26.0–36.3)	24.0 (21.2–33.9)	0.05
HbA1C, median (IQR), mmol/mol	113 (98–135)	116 (108–135)	0.52
HbA1C, median (IQR), %	12.4 (11.0–14.0)	12.8 (11.8–14.0)	0.32
Osmolarity, median (IQR), mmol/kg	325 (315–355)	330 (317–347)	0.88

HbA1C; glycated hemoglobin; DKA, diabetic ketoacidosis; T1D, type 1 diabetes.
*p .value significant

Table-4: Demographic Data of children newly diagnosed with T1D during the pandemic study period

Variables		With DKA Group I N=159	No DKA Group II N=53	P value
Age	Median IQR	7.2 (1.4-10.3)	6.7 (2-10.2)	0.170
Sex	Female sex, n (%)	26 (12.26)	21(9.91)	0.441
	Male sex n (%)	41 (19.34)	17 (8.09)	
RD	+Ve	113(53.3%)	18(8.49%)	< 0.0001*
	-Ve	46 (21.70%)	35(16.51%)	
Chest CT	+Ve	109(51.42%)	16(7.55%)	< 0.0001*
	-Ve	50(23.58%)	37(17.45%)	

DKA, diabetic ketoacidosis; T1D, type 1 diabetes. *p .value significant

Table-5: Laboratory parameters of the children newly diagnosed with T1D during the pandemic study period

Variable		With DKA Group I	Without DKA Group II	P value
		N=159	N=53	
RBS	Median IQR	285 (215-500)	215 (195-250)	0.010*
HBA1c %	Range Mean ± SD	(8.8-16.6) 12.4±2.5	(9.9-14.6) 11±4	0.496
pH	Range Mean ± SD	(6.4-7.1) 7.2±1	(7.3-7.5) 7.4±0	0.492
HCO3	Range Mean ± SD	(3-19.3) 9.8±5.6	(16-28.3) 20.3±3.5	<0.001*
CO2	Range Mean ± SD	(21-68) 48.7±14.2	(34.2-46.7) 42.9±3.8	0.015*
PO2	Range Mean ± SD	(44-126) 92.7±29.1	(19.6-72) 49±14.2	<0.001*
Lymphocytes	Median IQR	1400 (1000-2500)	2600 (1200-4500)	0.035*
Saturation	Range Mean ± SD	(60-98.9) 80±16.3	(65-87) 70.4±9.3	<0.001*
Result for nasopharyngeal SARS-CoV-2 RT-PCR) n (%)	+Ve -Ve	19 (8.96) 78 (36.79)	13 (6.13) 33 (15.57)	P=0.2705
Result for serum Covid antibodies (IgG and\or IgM) n (%)	+Ve -Ve	34 (16.03) 28 (13.21)	3 (1.42) 4 (1.89)	P<0.0001*

HbA1C; glycated hemoglobin; DKA, diabetic ketoacidosis; T1D, type 1 diabetes.
P.value significant

4- DISCUSSION

Since March 2020, the Pediatric Intensive Care Unit Department of Minia University Hospital, Minia, Egypt, has been facing an unprecedented outbreak of coronavirus disease and the spread of the 2019 novel coronavirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which had become a global pandemic (1, 10). Data from the early months of 2020 suggest a bidirectional relationship between COVID-19 and diabetes (9). During the COVID-19 pandemic, a total of 212 newly diagnosed T1D patients were admitted to our unit, of which 159 (75%) had DKA (Group I) and 53 (25%) did not (Group II). There was no variation in age or gender between the two groups (p=0.19, 0.24). There was a statistically substantial variation between the two groups as regards ABG profiles: HCO3, CO2, and PO2 (P=0.001, 0.015, and 0.001, respectively). At admission, there were 19 COVID-diagnosed patients (8.96%) who were also diagnosed with DKA, and 13 (6.13%) were diagnosed with hyperglycemia without DKA. While 34 (16.03%) patients with DKA and 3 (1.42%) patients with hyperglycemia only had positive results for serum COVID antibodies (IgG and/or IgM); this indicates that the rise in the number of children

receiving diabetes diagnosis and the more severe presentation of T1D were both primarily brought on by COVID. The number of children needing PICU admission for DKA dramatically rose by 159 (75%) throughout the COVID-19 pandemic at Minia University Hospital, and the rise in the overall number of children with new-onset diabetes was unanticipated. According to the 2020 research by Clemens et al., There are multiple precedents for a viral etiology of ketosis-prone diabetes, including coronaviruses that bind to ACE2 receptors (15). According to Clemens K. et al.'s 2020 study, an elevated incidence of diabetes was reported in patients with COVID-19, and diabetes predicts the degree of disease and death. Individuals with SARS coronavirus-a pneumonia reported to have greater rates of hyperglycemia and acute- are reported to have more diabetes than individuals with non-SARS pneumonia (15). Regarding the frequency of survivors and non-survivors during the study period, only two patients with diabetes and COVID-19 perished from severe respiratory symptoms, and their chest imaging revealed CORAD 3, because of a high viral load. Unsworth et al. (2020) discovered that patients with diabetes who had COVID-19 also had a greater non-survivor frequency rate (16). In a study on 138 patients, Elbarbary et al. (2020) found that compared to 37% of patients without comorbidities, 72% of COVID-19 patients with comorbidities-including diabetes-needed admission to the critical care unit (19). We saw a substantial rise in the frequency of children needing critical care for severe ketoacidosis in our retrospective cohort of children newly identified with T1D in the pandemic. Additionally, the number of children with newly discovered T1D increased. However, this elevation was unlikely to account for the rise in PICU admissions. Recent investigations in Italy, Germany, the United Kingdom, and Australia (17-19, 20, 21) reported an elevation in DKA in children with newly diagnosed T1D during the COVID-19 pandemic. In addition, a recent report from the United Kingdom (20) indicated that the rate of T1D in children had enhanced. In contrast, a research study performed in Germany found that the prevalence of T1D did not increase (22). All published research, except for study number, indicates that the clinical appearance of T1D has changed (23). A deteriorating clinical manifestation at the time of diagnosis may provide the erroneous impression that the prevalence of T1D is increasing without population-based research being carried out over a longer period. However, considering that the rate of T1D has been steadily dropping since 2010, the proportion of children with recently identified T1D has increased (24). To confirm that there has been a change in the rate of T1D, the follow-up time must be prolonged. Additionally, we cannot rule out the possibility that the epidemic impacted recruitment or participation at our facility. The connection between SARS-CoV-2 and a higher rate of T1D or a severe disease presentation requires further investigation. In susceptible individuals, viral infections can initiate the development of T1D. According to investigations using cell cultures, animal models, and organoid models, pancreatic beta cells contain the main SARS-CoV-2 entrance receptor ACE2, as well as the viral entry co-receptors transmembrane serine protease 2 (TMPRSS2) and neuropilin-1 (NRP1) (25-28). Additionally susceptible to SARS-CoV-2 infection were human beta cells derived from stem cells. A recent investigation examining various transcriptome datasets and human pancreatic tissue sections revealed 34 ACE2 and TMPPRS2 expressions in the pancreatic microvasculature and ductal cells but not in beta cells. This indicates that direct beta-cell toxicity mediated by ACE2 and

caused by SARS-CoV-2 is implausible. PCR detected SARS-CoV-2 in 2/21 newly diagnosed Type 1 diabetic children in the United Kingdom, and SARS-CoV-2 antibodies were discovered in 3/16 of the children examined (29). We did not employ a population-based methodology or a control group. Therefore, it is challenging to interpret these findings. Group-based long-term studies are necessary to corroborate these findings, since we discovered a comparable shift in the symptoms of diabetes in a group less impacted by the epidemic (30, 31). As it appears that more complex associations, such as those that affect the threshold at which families decide to get medical care, as well as the availability of health services have been involved, the rise in the number of children with DKA is most likely due to delays in the diagnosing T1D (32).

4-1. Strengths and Limitations of the study

Our research has limitations, since it was conducted at a single center. Despite this, we could provide coverage for every child in the region who needed intensive medical attention because they were all treated in the same healthcare system, which only had one PICU. Even though this research was conducted at a single center, we analyzed a substantial number of cases, due to this situation. Larger population-based studies with significantly longer follow-up periods are required to confirm the greater rate of T1D found in our research.

5- CONCLUSION

This clinical instance provides evidence for the significant association between COVID-19 infection and diabetes. Hence, medical practitioners must consider this in the case of nondiabetic children and conduct blood glucose and HbA1C screenings upon admission to provide timely and suitable interventions.

6- ETHICAL CONSIDERATIONS

The ethics committee authorized this research for the faculty of medicine, and all procedures were followed in accordance with the laws and regulations applied. Each parent gave a written permission to participate in the research. The participant's privacy and anonymity were maintained. The use of misleading tactics was avoided. The participants were allowed to leave the study at any time. A release for publishing was obtained.

7- AVAILABILITY OF DATA AND MATERIALS

The corresponding author may be reached on a reasonable request for the datasets utilized and/or analyzed in the present work.

8- CONFLICTS OF INTEREST

None.

9- REFERENCES

1. Papadokostaki E., Tentolouris N., Liberopoulos E. COVID-19 and diabetes: what does the clinician need to know? Primary Care Diabetes. 2020; 14(5):558–563. doi: 10.1016/j.pcd.2020.06.010.

2. Dong Y., Dong Y., Mo X., Hu Y., Qi X., Jiang F. Epidemiology of COVID-19 among children in China. Pediatrics. 2020; 145(6) doi: 10.1542/peds.2020-0702.

3. De Wilde A. H., Eric J., Snijder M. K., Van M. J. Assessment & Evaluation in Higher Education. New York, NY, USA: Springer International Publishing; 2012. Host factors in coronavirus replication; p. p. 435. Available from: http://books.google.com/books?id=_DDwCqx6wpcC&printsec=frontcover&dq=unwritten+rules+of+phd+research&hl=&cd=1&source=gbs_api%255Cnpapers2://publication/uuid/48967E01-55F9-4397-B941-310D9C5405FA%255Cnhttp://medcontent

.metapress.com/index/A65RM03P4874243N.p.

4. She J., Liu L., Liu W. COVID-19 epidemic: disease characteristics in children. Journal of Medical Virology. 2020; 92(7):747–754. doi: 10.1002/jmv.25807.

5. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat. Rev. Cardiol. 17, 543–558 (2020).

6. Mohamad IL, Saad K, Abdel-Azeem A, Mohamed SAA, Othman HAK, Abdel Baseer KA, Thabet AF, El-Houfey AA. Evaluation of pulmonary function changes in children with type 1 diabetes mellitus in Upper Egypt. Ther. Adv. Endocrinol. Metab. 6, 87–91 (2015).

7. Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, Sperling MA, Codner E. ISPAD Clinical Practice Consensus Guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr. Diabetes 19, 155–177 (2018).

8. Evans, K. Diabetic ketoacidosis: update on management. Clin. Med. J. R. Coll. Physicians Lond. 19, 396–398 (2019).

9. Chen Y., Gong X., Wang L., Guo J. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis MedRxiv. 2020. p. p. 280.

10. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, Boehm B, Amiel S, Holt RI, Skyler JS, DeVries JH, Renard E, Eckel RH, Zimmet P, Alberti KG, Vidal J, Geloneze B, Chan JC, Ji L, Ludwig B. Practical recommendations for the management of diabetes in patients with COVID-19. The Lancet Diabetes & Endocrinology. 2020; 8(6):546–550. doi: 10.1016/s2213-8587(20)30152-2.

11. Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, Mingrone G, Boehm B, Cooper ME, Chai Z, Del Prato S, Ji L, Hopkins D, Herman WH, Khunti K, Mbanya JC, Renard E. New-onset diabetes in COVID-19. The New England Journal of Medicine. 2020; 383(8):787–789. doi: 10.1056/NEJMc2018688.

12. Unsworth R, Wallace S, Oliver NS, Yeung S, Kshirsagar A, Naidu H, Wai Kwong RM, Kumar P, Logan KM. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the UK. Diabetes Care. 2020; 43(11):e170–e171. doi: 10.2337/dc20-1551.

13. Sathish T., Cao Y., Kapoor N. Newly diagnosed diabetes in COVID-19 patients. Primary Care Diabetes. 2020; 15(1):p. 194. doi: 10.1016/j.pcd.2020.08.014.

14. Jie Y., Jia S., Ng H., Yeoh E. Diabetic ketoacidosis precipitated by COVID-19 in a patient with newly diagnosed diabetes mellitus. Diabetes Research and Clinical Practice. 2020; 164 doi: 10.1016/j.diabres.2020.108166.108166

15. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020 Apr; 8(4):e21. doi: 10.1016/S2213-2600(20)30116-8. Epub 2020 Mar 11. Erratum in: Lancet Respir Med. 2020 Jun; 8(6):e54. PMID: 32171062; PMCID: PMC7118626.

16. Clemens KS, Matkovic J, Faasse K, Geers AL. Determinants of safety-focused product purchasing in the United States at the beginning of the global COVID-19 pandemic. Saf Sci. 2020 Oct; 130:104894. doi: 10.1016/j.ssci.2020.104894. Epub 2020 Jun 29. PMID: 32834513; PMCID: PMC7324098.

17. Kamrath C, Mönkemöller K, Biester T, Rohrer TR, Warncke K, Hammersen J,

Holl RW. Ketoacidosis in Children and Adolescents with Newly Diagnosed Type 1 Diabetes during the COVID-19 Pandemic in Germany. JAMA. 2020 Aug 25; 324(8):801-804. doi: 10.1001/jama.2020.13445. PMID: 32702751; PMCID: PMC7372511.

18. Lawrence C, Seckold R, Smart C, King BR, Howley P, Feltrin R, Smith TA, Roy R, Lopez P. Increased pediatric presentations of severe diabetic ketoacidosis in an Australian tertiary center during the COVID-19 pandemic. Diabet Med. 2021 Jan; 38(1):e14417. doi: 10.1111/dme.14417. Epub 2020 Oct 23. PMID: 33020999; PMCID: PMC7646057.

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 Nov; 21(7):1083-1092. doi: 10.1111/pedi.13084. Epub 2020 Aug 17. PMID: 32686287; PMCID: PMC7404589.

20. Gottesman, B. L., Yu, J., Tanaka, C., Longhurst, C. A. & Kim, J. J. Incidence of new- onset type 1 diabetes among US children during the COVID-19 global pandemic. JAMA Pediatr. 176, 414–415 (2022).

21. Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A; Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes. Has COVID-19 Delayed the Diagnosis and Worsened the Presentation of Type 1 Diabetes in Children? Diabetes Care. 2020 Nov; 43(11):2870-2872. doi: 10.2337/dc20-1321. Epub 2020 Aug 10. PMID: 32778554.

22. Tittel SR, Rosenbauer J, Kamrath C, Ziegler J, Reschke F, Hammersen J, Mönkemöller K, Pappa A, Kapellen T, Holl RW; DPV Initiative. Did the COVID-19 Lockdown Affect the Incidence of Pediatric Type 1 Diabetes in Germany? Diabetes Care. 2020 Nov; 43(11):e172-e173. doi: 10.2337/dc20-1633. Epub 2020 Aug 21. PMID: 32826282; PMCID: PMC7576433.

23. Atlas G, Rodrigues F, Moshage Y, Welch J, White M, O'Connell MA. Presentation Of Pediatric Type 1 Diabetes In Melbourne, Australia During The Initial Stages Of The Covid-19 Pandemic. J Paediatr Child Health. 2020 Oct; 56(10):1654-1655. doi: 10.1111/jpc.15081. Epub 2020 Sep 22. PMID: 32959935; PMCID: PMC7537060.

24. Parviainen A, But A, Siljander H, Knip M; Finnish Pediatric Diabetes Register. Decreased Incidence of Type 1 Diabetes in Young Finnish Children. Diabetes Care. 2020 Dec; 43(12):2953-2958. doi: 10.2337/dc20-0604. Epub 2020 Sep 30. PMID: 32998988.

25. Shi TT, Yang FY, Liu C, Cao X, Lu J, Zhang XL, Yuan MX, Chen C, Yang JK. Angiotensin-converting enzyme 2 regulates mitochondrial function in pancreatic β-cells. Biochem Biophys Res Commun. 2018 Jan 1; 495(1):860-866. doi: 10.1016/j.bbrc.2017.11.055. Epub 2017 Nov 9. PMID: 29128354.

26. Yang L, Han Y, Nilsson-Payant BE, Gupta V, Wang P, Duan X, Tang X, Zhu J, Zhao Z, Jaffré F, Zhang T, Kim TW, Harschnitz O, Redmond D, Houghton S, Liu C, Naji A, Ciceri G, Guttikonda S, Bram Y, Nguyen DT, Cioffi M, Chandar V, Hoagland DA, Huang Y, Xiang J, Wang H, Lyden D, Borczuk A, Chen HJ, Studer L, Pan FC, Ho DD, tenOever BR, Evans T, Schwartz RE, Chen S. A Human Pluripotent Stem Cell-based Platform to Study SARS-CoV-2 Tropism and Model Virus Infection in Human Cells and Organoids. Cell Stem Cell. 2020 Jul 2; 27(1):125-136.e7. doi: 10.1016/j.stem.2020.06.015. Epub 2020 Jun 19. PMID: 32579880; PMCID: PMC7303620.

27. Hasan NM, Kendrick MA, Druckenbrod NR, Huelsmeyer MK, Warner TF, MacDonald MJ. Genetic association of the neuropilin-1 gene with type 1 diabetes in children: Neuropilin-1 expression in pancreatic islets. Diabetes Res Clin Pract. 2010 Mar; 87(3):e29-32. doi: 10.1016/j.diabres.2009.12.016. Epub 2010 Jan 6. PMID: 20053475.

28. Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, van der Meer F, Kallio K, Kaya T, Anastasina M, Smura T, Levanov L, Szirovicza L, Tobi A, Kallio-Kokko H, Österlund P, Joensuu M, Meunier FA, Butcher SJ, Winkler MS, Mollenhauer B, Helenius A, Gokce O, Teesalu T, Hepojoki J, Vapalahti O, Stadelmann C, Balistreri G, Simons M. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science. 2020 Nov 13; 370(6518):856-860. doi: 10.1126/science.abd2985. Epub 2020 Oct 20. PMID: 33082293; PMCID: PMC7857391.

29. Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, Lee WW, Mungai LN, Rosenbloom AL, Sperling MA, Hanas R; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatr Diabetes. 2014 Sep; 15 Suppl 20:154-79. doi: 10.1111/pedi.12165. Epub 2014 Jul 12. PMID: 25041509.

30. Cherubini V, Gohil A, Addala A, Zanfardino A, Iafusco D, Hannon T, Maahs DM. Unintended Consequences of Coronavirus Disease-2019: Remember General Pediatrics. J Pediatr. 2020 Aug; 223:197-198. doi: 10.1016/j.jpeds.2020.05.004. Epub 2020 May 8. PMID: 32437758; PMCID: PMC7207102.

31. Rostami A, Sepidarkish M, Leeflang MMG, Riahi SM, Nourollahpour Shiadeh M, Esfandyari S, Mokdad AH, Hotez PJ, Gasser RB. SARS-CoV-2 seroprevalence worldwide: a systematic review and meta-analysis. Clin Microbiol Infect. 2021 Mar; 27(3):331-340. doi: 10.1016/j.cmi.2020.10.020. Epub 2020 Oct 24. PMID: 33228974; PMCID: PMC7584920.

32. Crawley E, Loades M, Feder G, Logan S, Redwood S, Macleod J. Wider collateral damage to children in the UK because of the social distancing measures designed to reduce the impact of COVID-19 in adults. BMJ Paediatr Open. 2020 May 4; 4(1):e000701. doi: 10.1136/bmjpo-2020-000701. PMID: 32420459; PMCID: PMC7223269.