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Evaluation of Serum COVID-19 IgG and IgM Antibodies Level in Pediatric Type 1 Diabetes Mellitus

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ABSTRACT

Background: As a result of the COVID-19 pandemic, healthcare providers are rethinking how they deliver care, interact with patients, and handle cases of diabetes in children in unprecedented ways. Family behavior may have increased diabetic ketoacidosis (DKA) due to the COVID-19 pandemic.

Objective: The purpose of the current study was to evaluate serum COVID-19 IgG and IgM antibodies level in pediatric type 1 diabetes mellitus (T1DM).

Patients and methods: A cross-sectional study was conducted on 36 patients newly diagnosed T1DM children presented by DKA or known diabetic exposed to DKA. The study was carried out between June and December of 2021/22 at Zagazig University's Paediatric Intensive Care Unit (PICU). COVID-19 IgG and IgM Antibodies were assessed among all patients.

Results: Antibodies differed significantly as regard DKA severity, Serum ferritin, D-dimer and CRP. Antibodies differed significantly as regard white blood cells and lymphocytes. The mean HbA1c was 8.99 (SD 0.97) with range from 7.2 to 11. There were 58.3% were newly diagnosed T1DM and 41.7% were known diabetic.

Conclusion: Evidence linked SARS-CoV-2 infection with T1DM. SARS COVID-19 IgG and IgM were detected in 36% of our studied group while the rest were negative for IgG and IgM.

Keywords: COVID-19, IgG, IgM, Antibody, Diabetes Mellitus.

INTRODUCTION

The coronavirus family is broad and diverse, causing conditions as diverse as the common cold and encephalitis. The 2019 COVID epidemic was triggered by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARSCoV2). Fever, coughing, shortness of breath, and muscle soreness are some of the common signs of COVID19 [(1)]. Over the course of the study period, a large cohort of Chinese patients with COVID19 demonstrated that illness severity can range from mild (81% of the time) to severe (14% of the time) to critical (5% of the time) (5%). Patients with critical illnesses accounted for all of the fatalities, and the case fatality rate was 2.3% overall [(2)].

Furthermore, another comprehensive review and meta-analysis found pooled rates of 11.9% for ICU admission, 18.4% for acute respiratory distress syndrome, and 4.3% for mortality [(3)]. The most common comorbidities associated with COVID-19 are diabetes, cardiovascular disease, and hypertension, according to several reports [(4)]. A statewide study in England found that people with any form of diabetes had a much higher risk of dying while receiving care at a hospital [(5)].

Still, it's encouraging to learn that young people, both those with and without diabetes, appear to be doing well in the face of COVID-19 infection [(6)]. No occurrences of type 1 or type 2 diabetes were found among the 2572 laboratory-confirmed cases in children and young adults under the age of 18 in the United States; instead, conditions like chronic lung disease and cardiovascular disease were more common [(7)], or absolutely no chronic illnesses at all [(8)].

Health care providers are implementing significant changes to health care systems, social services, and attitude and management of children living with diabetes in response to the COVID-19 pandemic, which has triggered profound shifts in the healthcare delivery environment [(9)].

The purpose of the current study was to evaluate serum COVID-19 IgG and IgM antibodies level in pediatric type 1 diabetes mellitus (T1DM).

PATIENTS AND METHODS

A cross-sectional study was conducted on 36 patients newly diagnosed diabetic children presented by DKA or known diabetic exposed to DKA. The study was carried out between June and December of 2021/22 at Zagazig University's Paediatric Intensive Care Unit (PICU).

Inclusion Criteria:

- Newly diagnosed diabetic children presented by DKA
- Known diabetic children presented by DKA
- Age from 1 year-18 years old.
- Both sexes were included.

Exclusion Criteria:

- Refusal of the parents.
- Age more than 18.

Methodology:

At the time of study enrollment, all patients had a comprehensive clinical evaluation (history and physical examination.

Full History

- Name, Age, Sex, Date of admission.
- Chronology of symptoms.
- Regular Insulin doses.

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- How often experiencing hypo or hyper glycaemia, what's trigger?
- Back ground diabetes control HbA1c.
- Co-existing medical condition.
- Social and family history.
- Immunization history.

Clinical examination:

- General: Weight, Height, BMI.
- Neurological: level of consciousness, headache.
- Respiratory: tachypnea, rapid shallow breathing.
- Cardio Vascular: Tachycardia.
- Gastrointestinal: Abdominal Pain, vomiting, diarrhea.

Lab. Investigation:

- Serum, IgG, IgM for COVID-19.
- Blood gases.
- Serum ferritin, D. dimer.
- HbA1c.
- CRP.
- CBC.
- Chest X-ray.

Intended Use:

The enzyme-linked immunosorbent assay (ELISA) kit for the indirect detection of IgM and IgG antibodies against COVID-19 virus in human serum is called the COVID-19 Human IgM IgG Assay Kit.

Ethical Approval:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (Approval No. #6886 24/05/2021). All children's parents gave their informed consent before being included in our study. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the all steps of the study.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test, Fisher's exact test and Monte Carlo test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean, median, standard deviation, and confidence intervals. Independent sample t-test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS

Table 1 summarizes the demographic data of the 36 recruited patients.

Table (1): Demographic data of the studied patients (n= 36)

Variable	No.	%
Gender		
Male	15	41.7
Female	21	58.3
Age (years)		
Min. – Max.	4 – 15	
Mean ± SD.	9.25 ± 2.81	
Median (IQR)	9 (7.5 – 11)	

There were 50.0% of the studied cases had mild DKA, 25.0% had moderate DKA and 25.0% had severe DKA (**Figure 1**).

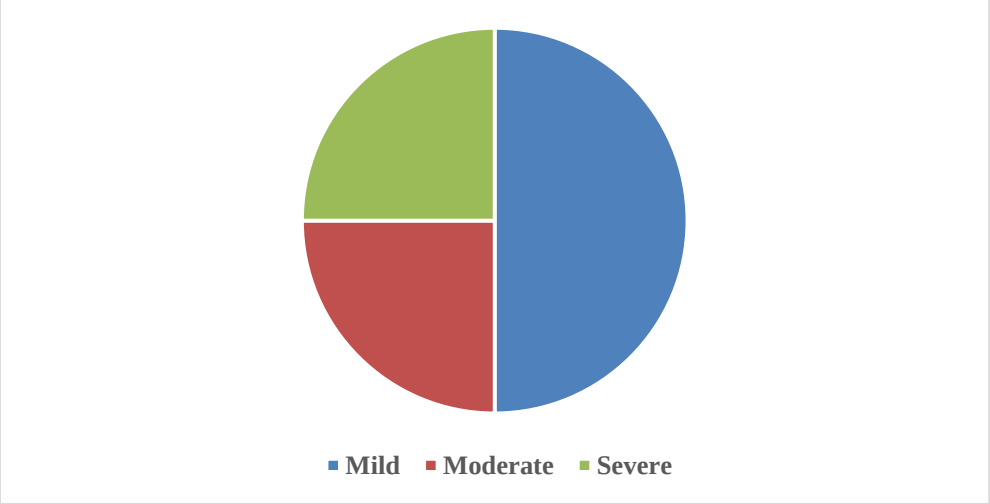

Figure (1): DKA severity among recruited cases.

Table 2 summarizes levels of Serum COVID-19 IgG and IgM among participants.

Table (2): Serum COVID-19 IgG and IgM among studied cases (n= 36)

Variable	No.	%
Status		
Negative	23	63.9
Positive	13	36.1
SARS COVID-19 IgG		
Mean ± SD	19.69 ± 4.73	
SARS COVID-19 IgM		
Mean ± SD	13.94 ± 3.12	

There were 58.3% were newly diagnosed diabetics and 41.7% were known diabetic (**Figure 2**).

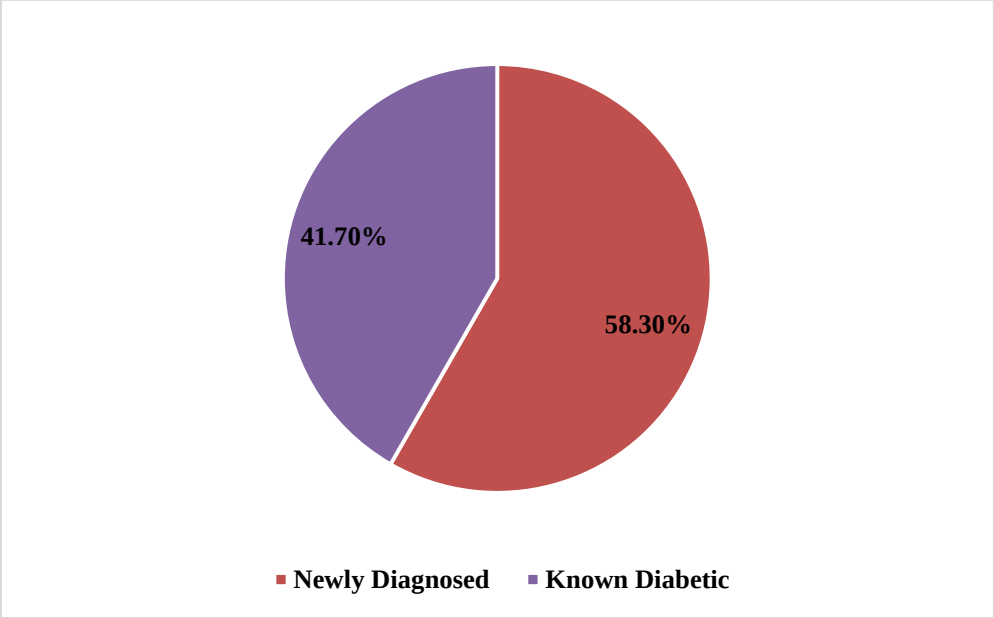

Figure (2): Newly diagnosed and known diabetic among studied cases.

Table 3 summarizes chest x ray findings of the studied cases.

Table (3): Chest X-ray distribution among studied COVID-19 cases (n= 36).

Chest x ray	No.	%
No	33	91.7
Yes (Ground glass appearance)	3	8.3

A statistically significant difference in DKA severity was found between COVID-19 antibodies (**Table 4**).

Table (4): Association between COVID-19 positive antibodies and DKA severity (n= 36).

DKA Severity	Antibodies				χ^2	MC P-value
	Negative (n= 23)		Positive (n= 13)			
	No.	%	No.	%		
Mild	18	78.3	0	0.0	29.005*	<0.001*
Moderate	5	21.7	4	30.8		
Severe	0	0.0	9	69.2		

MC: **Monte Carlo**

According to the results, there was no statistically significant difference between the antibody levels of people who had recently been diagnosed with diabetes and those who had been previously diagnosed as diabetic (**Table 5**).

Table (5): Association between positive COVID-19 antibodies and number (n= 36).

Variable	Antibodies				χ^2	P-value
	Negative (n = 23)		Positive (n = 13)			
	No.	%	No.	%		
Newly diagnosed	11	47.8	10	76.9	2.893	0.089
Known diabetic	12	52.2	3	23.1		

Statistically significant differences between antibodies were found in the table below for Serum ferritin, D-dimer, and CRP (Table 6).

Table (6): Association between positive antibodies with serum ferritin and D-dimer (n= 36).

Variable	Antibodies		Test of Sig.	P-value
	Negative (n = 23)	Positive (n = 13)		
Serum ferritin (ng/mL) Mean ± SD	564.96 ± 36.8	1203.9 ± 92.6	U= 13.0*	<0.001*
D-dimer (mg/L) Mean ± SD	0.75 ± 0.13	0.98 ± 0.02	t= 8.507*	<0.001*
CRP (mg/L) Mean ± SD	36.27 ± 6.70	60.6 ± 7.08	t= 10.258*	<0.001*

Table 7 demonstrates a statistically significant dissimilarity in the proportions of RBCs, WBCs, and lymphocytes that tested positive for an antibody.

Table (7): Association between positive antibodies and CBC (n= 36).

Variable	Antibodies		T test	P-value
	Negative (n= 23)	Positive (n= 13)		
Red Blood Cells (x 10^6/µL) Mean ± SD	4.43 ± 0.27	4.68 ± 0.45	2.129*	0.041*
Hemoglobin (g/dL) Mean ± SD	12.47 ± 0.99	12.57 ± 1.44	0.246	0.807
Hematocrit (%) Mean ± SD	38.83 ± 2.41	40.62 ± 3.31	1.871	0.070
MCV (fL) Mean ± SD	86.61 ± 4.24	89.38 ± 6.08	1.611	0.116
MCHC (%) Mean ± SD	33.78 ± 0.90	34.38 ± 1.12	1.761	0.087
White Blood Cells (x 10^3/µL) Mean ± SD	11.77 ± 2.21	11.79 ± 1.63	0.039	0.969
Neutrophils (x 10^3/µL) Mean ± SD	3.74 ± 0.92	4.49 ± 1.11	1.764	0.087
Lymphocytes (x 10^3/µL) Mean ± SD	3.69 ± 0.91	2.34 ± 0.54	3.465*	0.001*

DISCUSSION

The new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that produced the recently developed Corona Virus Disease-19 (COVID-19) has swiftly spread internationally, posing substantial health, socio-economic, and psychological risks18 to humanity. Many people with long-term conditions, such as diabetes mellitus, have been affected. There is no significant difference between the prevalence of diabetes in the general population and the prevalence of diabetes among COVID-19-affected people in adulthood **(10).**

Less is known about whether SARS-CoV-2 influences the incidence, seasonality, and severity of newly diagnosed T1DM in children and adolescents.

In a German investigation, researchers were unable to find evidence that the 2009 COVID-19 pandemic had any discernible effect on the rate of T1DM. On the other hand, the purpose of this study was to examine the impact of the brief German lockdown on the development of T1DM.

Therefore, given the brief duration of the pandemic, it is impossible to evaluate the effect of COVID-19 on the incidence of T1DM, and any potential changes in seasonal fluctuation. Another North American study found that among 48 children and young adults hospitalized to the PICU because of COVID-19, 8% were diabetic. While some research has found a link between diabetes and serious illness in kids, other studies have found no such correlation. The effect of COVID-19 on T1DM in children and adolescents is unclear because there are few comparative researches **(11).**

As regard demographic characteristics of studied cases; there were 41.7% of the studied cases were males and 58.3% were females. The mean age was 9.25 (SD 2.81) with range from 4 to 15. The mean weight was 38.19 (SD 5.31) with range from 27 to 50. The mean height was 151.4 (SD 12.06) with range from 123 to 173. The mean BMI was 17.08 (SD 1.18) with range from 15 to 20.

In the study of **Ata *et al.*** **(12)**, Patients with T1DM were on average 10.33 4.5 years older than controls, who were 10.35 4.8 years old (P= 0.843). There were 32 (56%) males and 25 (44%) females in the T1DM group, and 30 (49%) males and 31 (51%) females, respectively, in the control group (P= 0.441).

The present study showed that as regard DKA type among the study population; 50% of the studied cases had mild DKA, 25% had moderate DKA and 25% had severe DKA.

Whereas in the study of **Rabbone *et al.*** **(13)**, the incidence of DKA of any severity was 38.1% in 2020 (61/160) and 8.6% (86/208) in 2019 (all years combined) (41.3% [not significantly different]). While the percentage of newly diagnosed diabetics experiencing severe DKA was similar in 2020 and 2019 (16.9 and 14.9%, respectively), the percentage of patients experiencing severe DKA increased from 36.1 to 44.3% among those who presented in a state of DKA in 2020 (P= 0.03).

The present study showed that as regard chest x ray (ground glass appearance) presentation among the study population. There were 91.7% of the studied cases had no chest x ray findings and 8.3% had chest x ray findings which was consistent with previous studies held by **Wang *et al.*** **(14).** However, in a meta-analysis carried out by **Nassar *et al.*** **(15)** none of the included studies reported on the radiographic results of patients with COVID-19 and T1DM, they stated.

Many of the children brought to the PICU with DKA had been symptomatic for longer than patients in prior years, suggesting that diagnostic delays in T1DM are likely to account for the rise in the number of children with DKA. Patients with DKA who reported with symptoms including tachypnea, tiredness, or stomach pain were tested for COVID-19 even before receiving medical care. Thus, in our situation, the delayed diagnosis was not due to medical professionals confusing the signs of T1DM with those of COVID-19. More complicated relationships seem to have been at play, such as those that affect families' propensity to seek medical attention and the availability of health resources **(16).**

Our results showed that as regard measurements of SARS COVID-19 IgG and IgM among the study population. There were 63.9% had negative status and 36.1% had positive status. The mean SARS COVID-19 IgG was 19.69 (SD 16.82) with range from 9 to 67. The mean SARS COVID IgM was 13.94 (SD 6.06) with range from 9 to 33.

However, in the study of **Ata *et al.*** **(12)**, at the time of diagnosis, no positive results were found among those with T1DM on any of the available PCR tests. Five (8.7%) patients with T1DM and 6 (10%) controls had positive SARS-CoV-2 antibody tests.

Whereas **Salmi *et al.*** **(17)** showed that 33 kids' serum samples were collected during the epidemic. Seven days (interquartile range [IQR]: 5-10 days) passed between diagnosis and collection of serum samples. There was a first ELISA screening for SARS-CoV-2 spike IgG antibodies in all samples, and the results were negative in 32 of 33 cases. Although one sample tested positive for antibodies using ELISA, subsequent testing using the microneutralization technique showed no evidence of neutralizing antibodies.

The current study showed that there was highly statistically significant difference between positive antibodies cases and negative antibodies cases as regard DKA severity. From 13 positive antibodies cases 4 cases presented by moderate DKA and 9 cases presented by severe DKA but from23 negative antibodies cases18 cases presented by mild DKA and 5 cases presented by moderate DKA There was no statistically significant difference between positive antibodies as regard Newly diagnosed and Known diabetic. There was statistically significant difference

between positive antibodies as regard Serum ferritin and D-dimer. Where positive antibodies cases have higher serum ferritin, D-dimer and CRP than negative antibodies cases, there was no statistically significant difference between positive antibody cases as regard Red Blood Cells but as regard White Blood Cells. Positive antibody cases showed lymphopenia

In contrary to our results study of **González *et al.*** [18] as they reported that there were no variations in the expression of specific antibodies, and that there were also no variations in the expression of specific antibodies in relation to the severity of symptoms. The length of time symptoms persisted was positively correlated with antibody titers (r= 0.77). Disease severity and levels of control may account for the discrepancy between their study and ours.

In the study of **Ata *et al.*,** [12] the SARS-CoV-2 antibody test was positive in 5 (8.7%) patients with T1DM and 6 (10%) controls. Since patients denied experiencing COVID-19 symptoms, it was thought that this positivity was related to previous asymptomatic infection. The rate of positivity did not differ between the two groups (P= 0.901). Four (80%) of 5 SARS-CoV-2 antibody-positive patients were treated for DKA, 3 (60%) of whom had severe DKA.

CONCLUSION

Evidence linked SARS-CoV-2 infection with T1DM. SARS COVID-19 IgG and IgM were detected in 36% of our studied group while the rest were negative for IgG and IgM.

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