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Review Article

Looking into a New Challenge, DKA and Covid-19 A Review on Pediatric DKA Cases during New Coronavirus Pandemic Who is to Blame, the Virus or Health System?

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Abstract:

Since the first month of this new pandemic situation, all around the world healthcare system has been facing different challenges and difficulties; patients with chronic diseases such as cancer or diabetes with impaired immune system were at greater risk of infections and complications. It goes without saying that this issue was extremely important among pediatric clinicians dealing with diabetic pediatrics. Diabetes is the number one chronic illness among pediatric patients and the most dangerous and frightened complication of it is Diabetic Ketoacidosis (DKA).

Studies have shown a strong association between pandemic and increase in new diabetes type 1 cases and its lethal complication called DKA.

Here we are going to take a look at existing data and report about cases with this condition trying to find the missing piece of a big puzzle; what is the role of Covid-19 in causing Diabetes in previously healthy kids and what is the real association between SARS-COV2 virus infection and DKA?

We are going to review different studies, possible mechanism, new t1dm cases and old cases, with or without covid infection, DKA cases and its severity.

Key words: type 1 diabetes; diabetic ketoacidosis covid-19

Abbreviations: T1DM, DKA

Introduction:

Viral infections are fully described as a main factor contributing on the pathophysiology of type 1 diabetes mellitus (T1DM). There is extremely

rare data about the impact of COVID-19 T1DM and diabetic ketoacidosis (DKA) on paediatric patients [1].

Recent publications have shown the association between type 1 diabetes mellitus (T1DM) and increased morbidity and mortality rates during coronavirus disease (COVID-19) infection [2].

Diabetic ketoacidosis (DKA) is a life-threatening emergency in children and adolescents with manifestation of type 1 diabetes mellitus (DM1) [3].

The severe acute respiratory distress coronavirus 2 (SARS-CoV-2) has been reported to induce ketoacidosis and diabetic ketoacidosis (DKA) even in nondiabetic patients [4]. DKA is a lethal complication of T1DM. Specially in pandemic which newly diagnosed cases are increasing as much as more DKA cases. So we decided to take a closer look to this matter by reviewing current data.

Suggested mechanism

The severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) has been reported to induce ketoacidosis and diabetic ketoacidosis (DKA) even in previously healthy patients with no history of diabetes.

The pathophysiological mechanism of the SARS-CoV-2 infection can be discussed as different entities as mentioned here; hyperglycemia, and the exacerbated inflammatory cytokine storm [4].

SARS-CoV-2 causing COVID-19 uses angiotensin-converting enzyme 2 receptors for entry into cells, [5] these receptors are present on the surface of pancreatic islet cells. SARS-CoV has been reported to elevate blood sugar and result in a hyperglycemic state. One of the possible theory is that this virus can damage the pancreatic islet cells [2].

With the covid-19 outbreak an increase in pediatric Type 1 Diabetes Mellitus (T1DM) cases was reported. One of the possible explanations is the presence of autoantibody-induced immune dysregulation which is in fact caused by covid-19 [5].

Looking from a different view, it is crucial to take this in mind the social situation in pandemic and the delay to seek medical care can play a key role in this matter. Delay in diagnosis obviously cause critical complications to arise such as DKA [3]. other study also supported [9]. this hypothesis by reporting a meaningful increase in DKA among T1DM patients specially in countries with highest number of covid-19 cases [4].

In summary the mechanism underlying this phenomenon is for sure multifactorial. The factors related to viral nature and factors associated with healthcare system.

Patient with existing T1DM condition:

In one study conducted in Israel, it was demonstrated that among known pediatric cases of type 1 diabetes there was a significant increase in DKA during the first 3 months of pandemic. However in this multi centric retrospective study there was no significant difference in the severity of DKA in the setting of pandemic world. Please see the table [11].

In a report of 5 patients with 3 of them previously diagnosed with t1dm all 5 were tested positive for covid-19 and also presented with DKA (2 moderate 3 mild) [12].

Patients with newly diagnosed T1DM

In a study in Philadelphia children hospital 73 newly diagnosed cases were present only 2 of them were tested positive for Covid-19, the incidence of DKA was higher in the first three months of pandemic comparing to the same period of pre pandemic year but after that three months there was no significant difference, which is really interesting since it can support the hypothesis of delay in diagnosis and healthcare biases but also it can be related to limited data.

In a large Cohort study in Germany with 532 children new case of t1dm it was observed that diabetic ketoacidosis both in severe form and mild to moderate has been significantly higher compared with pre pandemic group, 238 patients developed Dka;but the study wasn't able to pinpoint an exact causality for its findings and it is assumed to be multifactorial [13].

In another study conducted in Saudi Arabia the results were in alignment of previous studies but one interesting fact was also reported.

They reported a number of 106 pediatric patients with new diagnosis of T1DM which had a higher risk of DKA by 26% comparing to pre pandemic group, the interesting part was they have found that the risk of developing DKA is actually higher in female and older children. They suggest that the underlying reason was in fact the because of lockdown and its consequence of delayed presentation [14].

In a study from Australian tertiary center 7 newly diagnosed t1dm were reported 5 presented with dKA, significntly higher compared to pre pandemic group. This study also considered delay

in seeking medical care as the culprit reason [8].

Another interesting report was from Turkey, as it is mentioned in the table was also reported 78 newly diagnosed t1dm with increased rate of DKA to 91% compared to 58% pre pandemic group but this study also showed autoantibodies association with DKA [15].

Country	**study**	**Sample size**	**Main findings**	**diabete**	**Covid-19 positive patients**	**Dka status**	Results
Germany	Cohort	532	During the COVID-19 period in 2020, the frequency of diabetic ketoacidosis was significantly higher compared with the 2 previous years (44.7% in 2020 vs 24.5% in 2019; severe diabetic ketoacidosis was also significantly higher compared with the previous years (19.4% in 2020 vs 13.9% in 2019;	Type 1	Not mentioned	238 103 severe dka	this study found a significant increase in diabetic ketoacidosis and severe ketoacidosis at diabetes diagnosis in children and adolescents during the COVID-19 pandemic in Germany
USA, CLEVELAND	single-centre retrospective	64	There was a higher prevalence of DKA on presentation during the COVID-19 time period compared to the pre-COVID-19 time period	13 newly diagnosed	Not mentioned	30 DKA 15 Mild 8 Moderate	this did not reach statistical significance in the new-onset group. Although the odds ratio confidence intervals of

	Cohort		(73% vs 47%). There was a significant worsening of DKA severity in the COVID-19 time	All type 1		7 severe	the new-onset group and established group overlapped, the higher overall rate and severity of DKA may have been driven by youth with previously established diagnosis of diabetes.
Turkey	Cohort	74	(DKA) cases increased from 58.7 to 91.9%. We found that celiac autoantibody positivity antibodies to glutamic acid decarboxylase (anti GAD) positivity, and islet cell antibodies (ICA), ICA and anti GAD positivity coexistence were higher in pandemic new patients	Type 1	None	70 dka cases 17 moderate 19 severe	We observed an increase in the number of patients newly diagnosed with type 1 diabetes mellitus, an increase in autoantibody positivity, and higher rates and severity of DKA during the COVID-19 pandemic period compared to the prepandemic period.
Romania	observational retrospective cohort study	147	Diabetic ketoacidosis at the onset of T1DM was 67.40% more frequent, and a higher percentage of these patients presented with a severe form	Type 1	8	97patients 41 severe Moderate 24 Mild 36	an increase in the incidence and severity of T1DM in children could be one of the consequences of COVID-19 pandemic
Saudi Arabia	multicenter retrospective cohort study	106	a remarkable increase of 11% in DKA frequency among children with T1DM during the lockdown period	Type 1	88of 106	20 cases of severe dka 2 of 20 were covid-19 positive	admission due to DKA incidence was higher among newly diagnosed T1DM in 2020 (Females and older children had a higher risk of developing DKA and severe DKA
Canada	Multicentric cohort study	260	presentation in DKA increased from 36.4% to 55.0% severe DKA from 37.0% to 48.3%	Type 1	Not mentioned	143 of 260 69 of 143 presented with severe dka	findings raise concern about access to appropriate and timely care during the COVID-19 pandemic.
Australia	Cohort	7	of severe DKA frequency was significantly higher in the pandemic period compared to the pre-pandemic periods (45% vs 5%; P <0.003), The overall frequency significantly higher during the pandemic period (73% vs 26%; P <0.007	Type1	none	5	We hypothesize that concern about presenting to hospital during a pandemic led to a delay in diagnosis. These data have important implications for advocacy of seeking healthcare for non-pandemic-related conditions during a global pandemic.
Usa , the Children's Hospital of Philadelphia	retrospective cohort	73	increased rates of dka in the first 6 weeks of the pandemic from March 16th to April 30th (63% in 2020 vs. 39% in previous years The total rates of ketoacidosis were similar to prior years in this group	Newly diagnosed type 1	2 of 68 tested	33	the increase in severe ketoacidosis was seen in those with government insurance. This possibly reflects an overall trend towards delayed presentation, but this study is limited by small patient numbers.
Alberta canada	retrospective chart review	107	The frequency of DKA at DM1 onset was significantly higher in the pandemic period (68.2% vs 45.6%; p < 0.001) and incidence of severe DKA was also higher (27.1% in 2020 vs 13.2% in 2019; p = 0.01).	Type 1	Not mentioned	73 severe dka	There was a significant increase in DKA and severe DKA in children presenting with new onset DM1 during the COVID-19 pandemic period

In Romania 147 newly diagnosed t1dm were reported and 8 of them were positive for covid-19 but 97 cases developed DKA [16].

In another interesting study in Alberta Canada, there was no significant difference between new cases in pandemic versus post pandemic but the

DKA prevalence was significantly higher by 68% compared to 45.6% [17].

Reports with both known and newly diagnosed cases

In a single center retrospective cohort study in Celeveland,USA of 64 patients 13 were newly diagnosed but both group showed a significant increase in presenting DKA comparing to control group from pre pandemic period [18].

Discussion:

DKA at diagnosis of T1DM is a life-threatening situation that represents the main cause of morbidity and mortality in pediatric patients with T1DM [19]. More children with T1D had severe DKA at diagnosis during the pandemic [20].

As the studies showed it is obvious that there is an increase in DKA and new cases with diagnosis of T1DM. In the table we provided here, it was tried to illustrate some of high impact studies which support the idea of pandemic causes new challenges for endocrinologists as managing new T1DM cases and most feared complication of DKA, worldwide;But the aim of this study was to shed light on the missing part of information, the WHY? We did our best to describe that this is multifactorial such as viral pathophysiology, but the key element here was understanding that our health policy and lockdowns and healthcare system around the world might be a double edge sword; as it was mentioned in most cases the cause was pointed to the delay of patients and clinicians to make the diagnosis.

Overall, our study faced some challenges like limited data, the gap of knowledge of exact pathophysiology mechanism responsible for.

In conclusion: T1DM and DKA are two important diagnoses in this pandemic that is better to be approached carefully by pediatricians and educating the public about not to delay to seek medical help seems to be necessary.

Further studies are needed to provide detailed information

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References:

1. Rao S, Ali K, Rivas M, Nugent K. (2021). Diabetic Ketoacidosis in Patients with COVID-19. The American Journal of the Medical Sciences. 361:668–669.
2. Kountouri A, Korakas E, Ikonomidis I, Raptis A, Tentolouris N, Dimitriadis G, et al. (2021). Type 1 Diabetes Mellitus in the SARS-CoV-2 Pandemic: Oxidative Stress as a Major Pathophysiological Mechanism Linked to Adverse Clinical Outcomes. Antioxidants (Basel, Switzerland).
3. Mönkemöller K, Kamrath C, Hammersen J, Biester T, Warncke K, Pappa A, et al. (2021). [Is it possible to prevent diabetic ketoacidosis at diagnosis of pediatric type 1 diabetes? Lessons from the COVID-19 pandemic]. Monatsschrift Kinderheilkunde : Organ der Deutschen Gesellschaft fur Kinderheilkunde. 1-8.
4. Eskandarani RM, Sawan S. (2020). Diabetic Ketoacidosis on Hospitalization with COVID-19 in a Previously Nondiabetic Patient: A Review of Pathophysiology. Clinical Medicine Insights Endocrinology and Diabetes. 13.
5. Tajiknia V (2021). A Brief Review on Covid-19 and Flavonoids Antiviral Effects. J Corona Virus. 1(3); 1-4.
6. Yang J-K, Lin S-S, Ji X-J, Guo L-M. (2010). Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetologica. 47:193-199.
7. Nielsen-Saines K, Li E, Olivera AM, Martin-Blais R, Bulut Y. (2021). Case Report: Insulin-Dependent Diabetes Mellitus and Diabetic Keto-Acidosis in a Child with COVID-19. Frontiers in Pediatrics. 9:628810.
8. Lawrence C, Seckold R, Smart C, King BR, Howley P, Feltrin R, et al. (2021). Increased paediatric presentations of severe diabetic ketoacidosis in an Australian tertiary centre during the COVID-19 pandemic. Diabetic Medicine : A Journal of the British Diabetic Association. 38:14417.
9. Hawkes CP, Willi SM. (2021). A trend towards an early increase in ketoacidosis at presentation of paediatric type 1 diabetes during the coronavirus-2019 pandemic. Diabetic Medicine : A Journal of the British Diabetic Association. 38:14461.
10. Danne T, Lanzinger S, de Bock M, Rhodes ET, Alonso GT, Barat P, et al. A Worldwide Perspective on COVID-19 and Diabetes Management in 22,820 Children from the SWEET Project: Diabetic Ketoacidosis Rates Increase and Glycemic Control Is Maintained. Diabetes Technology & Therapeutics. 23:632-641.
11. Jacob R, Weiser G, Krupik D, Takagi D, Peled S, Pines N, et al. (2021). Diabetic Ketoacidosis at Emergency Department Presentation During the First Months of the SARS-CoV-2 Pandemic in Israel: A Multicenter Cross-Sectional Study. Diabetes Therapy : Research, Treatment and Education of Diabetes and Related Disorders. 12:1569-1574.
12. Gorthi RS, Kamel G, Dhindsa S, Nayak RP. (2021). COVID-19 Presenting With Diabetic Ketoacidosis: A Case Series. AACE Clinical Case Reports. 7:6-9.
13. Kamrath C, Mönkemöller K, Biester T, Rohrer TR, Warncke K, Hammersen J, et al. (2020). Ketoacidosis in Children and Adolescents With Newly Diagnosed Type 1 Diabetes During the COVID-19 Pandemic in Germany. JAMA, 324:801-804.
14. Alaqeel A, Aljuraibah F, Alsuhaibani M, Huneif M, Alsaheel A, Dubayee M al, et al. (2021). The Impact of COVID-19 Pandemic Lockdown on the Incidence of New-Onset Type 1 Diabetes and Ketoacidosis among Saudi Children. Frontiers in Endocrinology. 12: 669302.
15. Dilek SÖ, Gürbüz F, Turan İ, Celiloğlu C, Yüksel B. (2021). Changes in the presentation of newly diagnosed type 1 diabetes in children during the COVID-19 pandemic in a tertiary center in Southern Turkey. Journal of Pediatric Endocrinology & Metabolism : JPEM.
16. Boboc AA, Novac CN, Ilie MT, Ieșanu MI, Galoș F, Bălgrădean M, et al. (2021). The Impact of SARS-CoV-2 Pandemic on the New Cases of T1DM in Children. A Single-Centre Cohort Study. Journal of Personalized Medicine; 11.
17. Ho J, Rosolowsky E, Pacaud D, Huang C, Lemay J-A, Brockman N, et al. (2021). Diabetic ketoacidosis at type 1 diabetes diagnosis in children during the COVID-19 pandemic. Pediatric Diabetes. 22:552-557.
18. Gera S, Longendyke RL, Minich NM, Malay S, Wood JR. (2021). The COVID-19 pandemic and associated worsening of diabetic ketoacidosis presentation in youth. Diabetic Medicine : A Journal of the British Diabetic Association. 38:14610.
19. Oyarzabal Irigoyen M, García Cuartero B, Barrio Castellanos R, Torres Lacruz M, Gómez Gila AL, González Casado I, et al. (2012). Ketoacidosis at onset of type 1 diabetes mellitus in pediatric age in Spain and review of the literature. Pediatric Endocrinology Reviews : PER. 9:669-671.
20. Salmi H, Heinonen S, Hästbacka J, Lääperi M, Rautiainen P, Miettinen PJ, et al. (2021). New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic. Archives of Disease in Childhood.