ESPE Physicians Information on COVID-19 and Pediatric Endocrine Diseases

This information is based on current knowledge of COVID-19 and will be updated as additional scientific evidence is released.

Disease specific information: Type 1 Diabetes Mellitus (T1DM)

In this review, we present a brief overview of the current knowledge on COVID-19 and its relationship with Type 1 Diabetes (T1D) in children and adolescents, and we provide recommendations as Pediatric Endocrinologists managing patients with endocrine disorders during the COVID-19 pandemic.

COVID-19 is caused by the virus, SARS-CoV-2. The virus shares phylogenetic similarity to the SARS coronavirus (SARS-CoV), the cause of the 2003 SARS outbreak. The virus spreads like any other respiratory infectious disease, through contaminated air-droplets of infected persons when talking, coughing, or sneezing. It can survive in the environment from a few hours to a few days, depending on surfaces and environmental conditions. The mouth, nose, and ocular mucosa appear to be the major source of transmission.

Does SARS-CoV-2 lead to T1D onset?

Viral infections have been implicated in the pathogenesis of T1D, acting as an environmental trigger that precipitates the presentation of the disease in genetically predisposed subjects [1]. In the case of SARS-CoV-2, it has been hypothesized that β-cell damage may be caused by viral entry mediated by the angiotensin converting enzyme 2 (ACE2), which is the receptor of the virus and is expressed on the surface of β-cells. Moreover, long-standing hyperglycemia has been found to reduce the expression of ACE2 (normally increased during the COVID infection), which is known to protect from the deleterious effect of inflammation [2,3]. Currently, the presence and the level of ACE2 expression in β-cells remains controversial. Moreover, analysis of pancreata from individuals infected with SARS-CoV-2 is not available to support the notion of direct β-cells infection. Additionally, rapid viral-mediated increases in

incidence are not very plausible, as fulminant autoimmune-mediated diabetes does not acutely present after infection.

Moreover, reports have not demonstrated, so far, an increase in the incidence of T1D. In Germany, the incidence rate of T1D per 100.000 children <18 years old was found to be 23.4, not significantly higher than the prediction of 21.1, calculated based on the number of children diagnosed with T1D from March till May since 2011. Although the incidence was higher compared to that of 2019 (16.4, p=0.04), the increase was attributed to the overall temporal trend of T1D over the last years [4]. In Italy, they observed a 23% reduction in the number of newly diagnosed children with T1D compared to 2019 [5]. On the other hand, a study from London did report an 80% increase in newly diagnosed children with T1D (corresponding to 12-15 more new cases), although the additional cases were only observed in two of the five participating units [6]. **Altogether, these three articles do not provide compelling evidence that the pandemic is leading to dramatic short-term adverse changes in incidence of pediatric T1D.**

Importantly, the number of children presenting with DKA was alarmingly increased. In 2020, 44.7% of newly diagnosed cases in Germany presented with DKA, whereas the percentage in 2019 for the same time period was only 24.5%. Of those, 43.2% were cases of severe DKA. Children younger than 6 years seem to be at greater risk [7]. Similarly, the proportion of cases with severe DKA in London was 52%, with 70% of the newly diagnosed children presenting with DKA [6]. Although, the last study did not show a delay in seeking medical advice after the presentation of alarming symptoms, it has been widely observed that the use of medical services has been significantly reduced in both adults and children during the first months of the COVID-19 epidemic, possibly leading to the development of ketoacidosis [8,9].

Does Diabetes predispose children to SARS-CoV-2 infection?

Adults with certain underlying medical conditions, including diabetes, are at increased risk of severe illness from COVID-19. In contrast to adults, diabetes does not appear to predispose children with T1D to COVID-19 infection. In fact, no cases of diabetes were reported in 2572 COVID-19 confirmed cases of children <18 years old in USA [10]. Moreover, although adults with T1D seem to be at an increased risk for severe COVID -19, the severity of the clinical course seems to be mostly related to age, poor glycemic control and the presence of diabetes complications and comorbidities [11], explaining thus the milder course of the disease in

children with T1D. However, as with all infections, COVID-19 may lead to glycemic dysregulation. Data from the T1D Exchange-Q1 study which included 64 people with T1D and confirmed or suspected COVID-19 infection aged 7-79 years old (mean age: 20.9) demonstrated that 50% had persistent hyperglycemia as the presenting symptom and 30.2% of them had DKA during the course of the infection [12]. However, results from strictly pediatric populations are much more reassuring. **Overall, the accumulating evidence suggests that children with T1D infected with SARS-CoV-2 have similar disease outcomes as peers without diabetes.** Given that obesity and hypertension are associated strongly with type 2 diabetes in youth and these comorbidities have been associated with more severe COVID-19 cases, children with type 2 diabetes may be at higher risk. Country-wide surveillance and reporting systems need to be implemented for children with T2D.

What changes occurred in pediatric diabetes care?

In fact, it is extremely encouraging and reassuring to observe that, despite extremely stressful and burdening conditions, such as the quarantine, children with T1D have exhibited excellent coping skills. In a study of 264 children with T1D, especially those >12 years old reported more active involvement in glucose monitoring and engaged in physical activity even indoors [13]. A smaller study of 22 children (mean age 8.7 ± 1.9 years) showed higher "Time in Range", lower "Time Above Range", increased bolus insulin doses and less time spent in hypoglycemia during the quarantine compared to the pre-COVID period. The authors attributed the improvement of glycemic control to the active parental involvement in the care of diabetes, including the familiarization with the devices that have dramatically changed the management of T1D (mainly CGMS systems), the careful observation and the interpretation of the data offered by them [14]. Similarly, in another Italian study, children with T1D had similar but less episodes of DKA and severe hypoglycemia compared to the same period in 2019 [5].

What should patients do during the COVID-19 pandemic?

Maintaining good glycemic control is of outmost importance throughout this pandemic, to avoid being infected but also to avoid severe diabetes complications or a more severe course of the disease in case of infection. Frequent measurements or intense use of CGMS systems, achieving glycemic targets, engaging in physical activity even indoors and making healthy food

choices are strongly encouraged. Adhering to the general rules for the protection from the coronavirus, including social distancing, use of facial masks, thorough hand washing, and avoidance of face touching and meticulous disinfecting of surfaces, is warranted. In case of COVID-19 infection the family needs to implement the principles of "sick day management". These principles include more frequent glucose and ketone measurements, administration of insulin in all cases, adaptation of insulin doses to the increased insulin requirements, maintaining good hydration and providing symptomatic treatment. The family should remain alert for any symptoms that are suggestive of DKA, including vomiting, fruity odor of breathing difficulty, abdominal pain, lethargy, or confusion. If DKA is suspected, seeking immediate medical advice, either by contacting the diabetes team or by visiting the closest Emergency department is encouraged. Avoiding transition to a medical facility due to the fear of the coronavirus might have detrimental consequences. Primary health care physicians should also not hesitate to refer a child with suspected diabetes to a specialized center [15–18].

Maintaining regular contact with the diabetes team is essential. In the light of the COVID-19 pandemic, the use of technology has made the "digital" management of diabetes possible, minimizing thus the need for physical presence at the diabetes clinic. Data from insulin pumps, sensors, glucose meters, dosage advisors can be downloaded and subsequently sent via mail or even directly uploaded to the cloud and shared with the members of the diabetes team who can provide feedback. Online meeting platforms have also enabled the communication of the team with the child and the family, so as to achieve a more efficient consultation [19]. Groups of children or parents on social media platforms have also provided practical advice and comfort during these difficult times. Undoubtedly, easy and safe data exchange, secure data storage and protected access with respect to relevant regulations need to be ensured for the successful use of telemedicine in the management of T1D.

Public data on new-onset incidence trends

Data scarcity regarding many aspects of how COVID-19 is affecting children with both new-onset and established diabetes is a concern.

To date, all studies on new-onset diabetes, both type 1 and type 2, in both children and adults with SARS-CoV-2 (COVID-19) infection are not conclusive. The subject has been limited by small sample sizes and the fact a diagnosis of COVID-19 could not always be confirmed. In order to address these limitations, an International group of leading diabetes researchers set

up a global registry of COVID-19–related diabetes with the aim to establish the extent and nature of new-onset diabetes and the outcomes of diabetes in the context of COVID-19. The COVIDIAB Global Registry http:// COVIDiab.e-dendrite.com/# is already accepting data on new cases from major centres around the word including from countries where the pandemic is at its height as Latin America, Brazil, India and Africa.

When will children be able to get the COVID-19 vaccine?

Vaccine to prevent COVID-19 caused by SARS-CoV-2 is administered as a 1 or 2-dose series.

Pfizer/BioNTech and Moderna are already testing the vaccine in children, and Johnson & Johnson plans to do the same. Currently, the Pfizer/BioNTech COVID-19 vaccine is authorized for use in children 16 years and older, while the Moderna and Johnson & Johnson vaccines are authorized for people 18 years and older.

Pfizer/BioNTech and Moderna are conducting studies, in which the vaccines are tested in groups of children of descending age. The companies are currently testing its vaccine in children ages 12 to 15. According to preliminary results, vaccine trials for children ages 5 to 11 will be next. Data from the age de-escalation studies might be available by the summer 2021.

Moderna is starting to test their vaccine in children ages 12 to 17. They eventually plan to test their vaccine in children as young as 6 months.

It could be assumed that children affected with T1DM would not be classified as a risk group for vaccination.

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Improving the clinical care of children and adolescents with endocrine conditions, including diabetes, through research and education

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