



Guest Editorial

# COVID-19 pandemic and new-onset diabetes mellitus – The evidence for a causal relationship

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Life was interrupted in many ways during the pandemic years of 2020–2022, and the degree of lockdown varied between countries. Case reports and later observational studies have been noticing an increase in the number of children with new-onset diabetes. In this issue of the Journal of Pediatric Endocrinology and Diabetes, Montgomery and associates report a 38% increase from their center during the pandemic in 2021, with the highest rate in the youngest.<sup>[1]</sup> This is an issue which has been much debated in recent years.

In a nationwide Scottish study, there was a clear peak in 2021 in the 6–14 year-old children that regressed in 2022, while such a pattern was not seen in younger or older children.<sup>[2]</sup> Portuguese register data on 574 new-onset young persons (92% <18 years of age) did not reveal an overall statistically significant increase in incidence, while two centers did find an increase.<sup>[3]</sup> In Israel, the COVID-19 pandemic was associated with a significant increase in the incidence of new-onset type 1 diabetes (T1D) in prepubertal and pubertal children.<sup>[4]</sup> Anti-COVID-19 vaccination decreased the incidence rate significantly only in pubertal children.

An increase in incidence during the epidemic as well as diabetic ketoacidosis (DKA) being more common and more severe was found both in Malaysia,<sup>[5]</sup> Turkey,<sup>[6]</sup> and Iran.<sup>[7]</sup> A regional study in Germany found an increase from prepandemic incidence of 17.6/100,000 in 2002–33.2 in 2022 in T1D and from 2.8 to 6.4/100,000 in type 2 diabetes (T2D).<sup>[8]</sup> In Thailand, the T1D incidence remained stable during the COVID-19 pandemic, while a significant rise in T2D incidence was observed.<sup>[9]</sup> Data from a single center in China showed an increase in DKA in the first pandemic year 2020, that returned to prepandemic levels the next year.<sup>[10]</sup> There was a 5% yearly increase in T1D diagnosis up until 2020, but in 2021 and 2022 the incidence declined. However, there was no increase in DKA in an Argentinian study.<sup>[11]</sup>

One would probably expect a decrease again to prepandemic levels afterwards. This was seen in the Scottish study during pandemic year 3.<sup>[2]</sup> A decrease in incidence after the pandemic was also reported in a US study on type 2 diabetes.<sup>[12]</sup> There was also a slight increase in body mass index (BMI) and BMI standard deviation scores, observed before the pandemic and continued during the pandemic years.<sup>[13]</sup>

Healthcare delay was common during the pandemic in that many people were not keen on being tentatively exposed to COVID while in the emergency room waiting room. This may account for a more severe presentation with DKA,<sup>[14]</sup> which was also found in a German study.<sup>[15]</sup> Diabetes is listed as one of the risk factors for critical COVID-19 illness with worse outcomes.<sup>[16]</sup> Omicron has been found to be associated with a higher affinity to  $\beta$ -cell entry receptor and a lesser cytokine

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release.<sup>[17]</sup> However, an increase in DKA during the Omicron phase was only prominent in Africa<sup>[18]</sup> but not in China.<sup>[19]</sup> Cai *et al.*<sup>[14]</sup> list a number of confounding factors that can affect the incidence: Data from ethnic subgroups are often not reported. Glucocorticoids given during the treatment course can trigger diabetes onset. Vaccination status and polymerase chain reaction data are often not reported or unavailable.

As mentioned above, many studies have found an increased incidence of T1D during the pandemic. If this were a causal association, one would expect a decrease to prepandemic levels or even lower afterwards (assuming that COVID-19 triggered persons in pre-diabetic stages present with overt hyperglycemia). Indeed, a European study including centers from 7 countries in children having a >10% risk for developing autoimmunity by the age of 6 years did have a two-fold increase in islet autoantibody incidence, but not until after the pandemic.<sup>[20]</sup> However, a German register study with 9596 new-onset cases concluded that a causal relationship between Severe acute respiratory syndrome coronavirus 2 infection and T1D among children and adolescents is unlikely.<sup>[15]</sup> A US study including both T1D and T2D likewise found an increase in the incidence of T1D during the pandemic but was not able to demonstrate a significant correlation between COVID-19 infection and new-onset diabetes.<sup>[21]</sup> In Sweden, national register data showed an increase in incidence by 17% (from 41.5 to 58.5/100,000) in 2021 and 2022, returning to prepandemic levels in 2023. However, this increase was mainly seen in boys who had a lower than expected frequency of antibody negativity.<sup>[22]</sup> An increased progression from presymptomatic diabetes to an overt onset was confined only to those individuals with positive COVID-19 in a German study.<sup>[23]</sup>

In conclusion, the case is still open. There are many observations of an increase in incidence both in T1D and T2D during the pandemic, but the evidence of a causal relationship is not yet convincing, and further research is required. It remains to be studied if COVID-19 vaccination in presymptomatic individuals could prevent or delay the diabetes onset.

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