



# COVID-19 and Type 1 Diabetes: Addressing Concerns and Maintaining Control

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The worldwide outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been an unprecedented pandemic. Early on, even as the signs and symptoms of coronavirus disease 2019 (COVID-19) were first characterized, significant concerns were articulated regarding its potential impact on people with chronic disease, including type 1 diabetes. Information about the basic and clinical interrelationships between COVID-19 and diabetes has rapidly emerged. Initial rapid reports were useful to provide alerts and guide health care responses and initial policies. Some of these have proven subsequently to have durable findings, whereas others lacked scientific rigor/reproducibility. Many publications that report on COVID-19 and “diabetes” also have not distinguished between type 1 and type 2 (1). Available evidence now demonstrates that people with type 1 diabetes have been acutely affected by COVID-19 in multiple ways. This includes effects from limited access to health care, particularly during lockdown periods, and increased morbidity/mortality in infected adults with type 1 diabetes compared with peers without diabetes.

## MIGHT COVID-19 CAUSE OR ACCELERATE TYPE 1 DIABETES?

At present, there is not convincing evidence that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exacerbates or induces persistent diabetes. A small initial report suggested concerning increases in type 1 diabetes incidence concurrent with the pandemic (2). Later population-based reporting did not confirm this observation (3). Rather, data suggest that affected individuals and their caregivers delayed accessing care at the time of diagnosis (4) and that primary care offices were shut down when acute care centers were open, leading to greater numbers of people presenting more acutely to hospital settings. It is possible but not proven that the cytokine storm that is common in coronavirus disease 2019 (COVID-19) may also injure or stun the limited  $\beta$ -cell reserve in individuals nearing stage 3 of type 1 diabetes, accelerating the last weeks of acute disease presentation. Although there were early concerns that the SARS-CoV-2 angiotensin converting enzyme coreceptor (ACE) and the required transmembrane serine protease (TMPRSS) cofactors for cellular entry might be found in insulin-producing  $\beta$ -cells and that these cells might be susceptible to viral infection, later immunohistochemistry pancreatic work did not confirm these findings (5,6). It is also unlikely that during active infection these receptors are induced in  $\beta$ -cells (7).

Will the pandemic acutely or chronically change epidemiology of type 1 diabetes? This question has been raised since a few viral illnesses have been suspected to induce or accelerate type 1 diabetes. Evidence to date suggests that it is unlikely that the SARS-CoV-2 infection either induces autoimmunity or causes permanent

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**See accompanying articles, pp. XXXX and XXXX.**

$\beta$ -cell damage (7). However, given that we now recognize many endotypes of type 1 diabetes, further surveillance is needed to determine if a subset of people develops type 1 diabetes after SARS-CoV-2 infection. Decreases in other circulating endemic and seasonal viral infections due to public health guidelines to mask and wash hands might also reduce presentation of autoimmune diseases, although larger future endemic infectious outbreaks are also possible (8).

### RISKS FROM COVID-19 FOR PEOPLE WITH TYPE 1 DIABETES

There does not appear to be any increased susceptibility to SARS-CoV-2 infection for individuals with type 1 diabetes (9,10). Generally, people with type 1 diabetes present with similar COVID-19 symptoms as those in the general population: dry cough, nausea, vomiting, fever (11).

Yet, once an adult with type 1 diabetes is infected with SARS-CoV-2, they are at increased disease-related risk. Overall, adults with type 1 diabetes have odds similar to those for people with type 2 diabetes for severity of illness, hospitalization, and in-hospital mortality (12). COVID-19 may initially present with concurrent hyperglycemia and even diabetic ketoacidosis (DKA). Some of the typical COVID-19 symptoms (nausea/vomiting) may also mask the DKA onset, delaying DKA diagnoses and further worsening prognosis (13).

Certain intra-individual factors translate into increased risk for infected individuals with type 1 diabetes. For starters, older age, which also affects the likelihood of long-term complications or death from COVID-19 in the general population, appears to be the greatest risk factor for hospitalization and illness severity for adults with type 1 diabetes. French population-based analyses (the CORONADO study) showed higher mortality in older patients with COVID-19 and type 1 diabetes compared with patients without type 1 diabetes (14). In CORONADO, the risk for younger patients with type 1 diabetes was less; for example, among individuals <55 years of age, 12% of those with type 1 diabetes died or required intubation within the first week of hospitalization compared with 30% of individuals with type 2 diabetes. Another U.S.-based

study (that combined type 1 diabetes and type 2 diabetes) found that illness severity nearly doubled for each 25-year increase in age (12). Additional information about how much of the impact of “older age” is in fact “duration of diabetes” is needed.

No present evidence suggests that youth with type 1 diabetes have higher mortality or morbidity, including risk of hospitalization, than healthy peers (15,16). Reports that suggest otherwise that are based on small sample sizes subject to type I error and publication bias or fail to consider confounders such as acuity of hospitalization (17,18). They should not be used as the basis for public health messaging. Confusion about the difference between “autoimmune” disease and “immune deficiency” has also produced unwarranted concerns.

Glycemic control at the time of infection may also play a role in outcomes. One U.K. study reporting on deaths in 463 individuals (56.6% male) with COVID-19 and type 1 diabetes suggested a higher mortality risk in those with an  $HbA_{1c} > 10\%$  (86 mmol/mol, hazard ratio 2.23 [95% CI 1.5–3.3,  $P < 0.0001$ ] [19]). Poor glycemic control is known to be associated with more serious infection in other settings (20); in individuals with COVID-19, it may amplify the hyperimmune response (21). COVID-19 itself also can impair any remaining endogenous insulin secretion and reduce glucose disposal by inducing inflammation and cytokine production. Additionally, individuals with COVID-19 may be volume depleted, immobilized, treated with steroids, and/or experience acute kidney injury (7)—all of which can also worsen glycemia.

Other factors in adults with type 1 diabetes appear to worsen risks from COVID-19. Those who are non-Hispanic Black, use public insurance, and have hypertension are more likely to be hospitalized for COVID-19 infection (22). Obesity also likely increases the risk (23), whereas insulin pump and continuous glucose monitor use may be mitigating factors (12).

Since  $HbA_{1c}$  tends to remain relatively stable in adults over time (24), individuals with higher  $HbA_{1c}$  at the time of SARS-CoV-2 infection also have a higher likelihood of longer-term hyperglycemia and concomitant diabetes-related vascular disease. COVID-19

has clear vascular effects. For people with type 1 diabetes and underlying micro- and macrovascular disease, the disease course is likely worsened due to the inflammatory, endothelial dysfunction, and prothrombotic effects of SARS-CoV-2 infection. Indeed, diabetic retinopathy has recently been described to be independently associated with risk of intubation in hospitalized COVID-19 patients (25). The risk of mortality also appears to be increased in individuals with vascular diabetes-associated complications (19,26). This vascular aspect of COVID-19 likely explains why children with type 1 diabetes are relatively protected from severe illness; i.e., children with type 1 diabetes are more like other children from a vascular and risk perspective than they are like adults with long-standing type 1 diabetes.

Increased risk recognition has gradually translated into governmental advice for caution for adults living with type 1 diabetes. The Centers for Disease Control and Prevention has released information on which individuals in the U.S. should take extra precautions related to COVID-19 (27). Initially, that guidance, based on a preponderance of available information from individuals with type 2 diabetes (9) without considering newer information about type 1 diabetes, suggested that people with type 2 diabetes are at increased risk of severe COVID-19 illness, whereas type 1 diabetes “might” increase the risk of severe illness. This policy was revised in late March 2021. In contrast, the U.K. Joint Committee on Vaccination and Immunization SARS-CoV-2 vaccine policy more appropriately stated from its start that individuals with both type 1 and type 2 diabetes are considered at clinical risk for more severe disease (28).

### CARE CONSIDERATIONS FOR COVID-19 AND TYPE 1 DIABETES

At present, the overall public health advice for people with type 1 diabetes during the pandemic is equivalent to that of the general population: wear masks, follow social distancing guidelines, eschew nonessential travel, and avoid indoor gatherings whenever possible. This is particularly important as more-transmissible and potentially less-vaccine-susceptible SARS-CoV-2 variants are circulating. Additionally, given the

association of worse COVID-19 outcomes for people with poorer glycemic control, individuals with type 1 diabetes should do what is possible and necessary to optimize glycemic control, targeting an HbA<sub>1c</sub> of <7%. Some data suggest worsening of glycemic control in adults with type 1 diabetes during lockdown periods (29), which is potentially associated with greater stress and anxiety, less exercise, and weight gain (30). Additionally, DKA risk during this pandemic time appears to be heightened even for people with type 1 diabetes who are not infected with SARS-CoV-2, most likely due to delays in accessing care (31,32).

The pandemic has also adversely affected research aiming to prevent, cure, and ameliorate type 1 diabetes. The pandemic has put immunotherapy trials seeking to prevent or reverse type 1 diabetes on indefinite hold and reduced participant entry rates into ongoing trials (33) of other agents. As an example, the Type 1 Diabetes Trial-Net network, following advice from its infectious disease committee, has put a prevention study using rituximab (anti-CD20) and abatacept (CTLA-4-Ig) (NCT03929601) on indefinite hold. The funding streams for organizations committed to curing and improving care for people affected by type 1 diabetes have been significantly impacted, with the biggest impact on the not-for-profit organizations American Diabetes Association and JDRF, who have cut funding opportunities and staffing (34,35).

Coronavirus vaccines are being distributed to ever-widening groups of individuals around the nation and the world. People with diabetes (not distinguishing between type 1 and type 2) were included in all the major trials without suggestions of decreased vaccine effectiveness for individuals with diabetes (36,37). With the advent of this public health advance comes a series of decisions and concerns given the limited rate of vaccine distributions, and many efforts to prioritize the highest-risk groups. The Centers for Disease Control and Prevention initial guidance indicating differences in risk of COVID-19 by type of diabetes led to some states inappropriately excluding people with type 1 diabetes from the high-risk categories of individuals getting access to vaccine. Advocacy around improving access to the vaccine for

people with type 1 diabetes is critical and actively underway (38). In general, people with type 1 diabetes should seek out and receive effective vaccines as soon as possible and permitted based on local guidelines.

### LOOKING TO THE FUTURE

There have been some bright spots in this pandemic for the care of people with type 1 diabetes. The pandemic provided an incentive for considerable expansion of telemedicine (39). Data suggest that telemedicine can be beneficial for management of children and adults with type 1 diabetes (40). Although at first virtual visits were performed out of urgent necessity to provide care, over time they have become part of the fabric of diabetes centers. Even after this pandemic, telemedicine offers an opportunity to provide additional touchpoints for the highest-risk people with diabetes and provide more clinical care without taxing further limited physical clinical space. Telemedicine may also ultimately increase the efficiency and cost-effectiveness of the care. Full incorporation of telemedicine will require advocacy for maintained payor coverage of virtual care, deliberate planning to permit interstate care delivery, intentional work to offer this to people with type 1 diabetes with limited technology access, and general acceptance of glycemic metrics that can be obtained by remote downloads (e.g., time in range, glucose management indicators) as an alternative quality measure to laboratory measures of HbA<sub>1c</sub>.

The pandemic also accelerated the use of continuous glucose monitor based remote monitoring of glycemia. In the hospital, it began to be used more routinely for people with diabetes who were being cared for to reduce care provider exposure to virus (41). In the ambulatory care setting, it permitted remote monitoring of care when patients were unable to attend in-person clinical visits. Concomitant with this is an apparent rise in the “literacy” of both patients and caregivers to download devices and upload reports from home. Ongoing technical support will be needed for patients and providers lest this ability for remote monitoring widens the observed racial and

socioeconomic disparities in care for persons with type 1 diabetes (42).

An additional pivot that has happened amid this pandemic is the change to virtual scientific meetings. This includes the change of several large diabetes meetings where scientists and others who care for people with type 1 diabetes gather to exchange data and ideas. Although this pivot has certainly had its downsides, particularly for junior faculty who are not able to network as readily with senior scientists in their fields, it has also permitted wider audiences for some meetings and has enabled people with other obligations (e.g., child care) that might have prevented them from being able to attend remote meetings in person to be engaged. Early data suggest that a move to virtual meetings may have improved representation of women as session chairs and invited speakers (43).

Although there were initial concerns about access to needed supplies and insulin, overall, children and adults with type 1 diabetes without COVID-19 who were in “lockdown” at home did not experience acute deterioration in their glycemic control or overall care, and some even saw improvements. Some of this was likely due to increased time for attention to diabetes (44), some due to more consistent food and sleep intake, and some due to lower physical activity (45); some may have been due to fewer circulating viruses and less intercurrent illness. Other data, particularly for children, suggest improvements in glycemic control in some groups, potentially due to greater parental/caregiver supervision of care (46).

### CONCLUSIONS

It is essential that we continue to both evaluate and report on outcomes of people with type 1 diabetes during this unprecedented pandemic period and that we base public health recommendations on the best available quality data. This is especially critical for advocating clearly about the need for all with type 1 diabetes to be vaccinated while still deliberately and clearly messaging to parents and caregivers about the more limited risks to our youngest patients as we work to optimize their glycemic control. We need to continue to work to ensure everyone worldwide

with type 1 diabetes has access to insulin and other needed diabetes supplies, even when health care systems are stressed by waves of affected individuals and supply-chain disruptions. We should also continue to monitor for the possibility of particular “long COVID” effects for people who also live with type 1 diabetes (47). Efforts such as the CoviDiab Registry (CoviDiab.e-dendrite.com) are critical. As always, we should work with patients and their families to nurture their resilience and coping skills, even in the face of significant challenges.

As of this writing, hope is on the horizon. Mass vaccination efforts for adults are ramping up worldwide. Trials to evaluate safety and efficacy for vaccines in younger children are ongoing. Ultimately, more research is needed on the acute and long-term effects of COVID-19 on people with type 1 diabetes, as well as how the pandemic and the accompanying changes in environmental and infectious disease exposures impact future rates of presentation of autoimmune conditions such as diabetes.

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