



Relationship between Diabetes and COVID-19

Since the beginning of the COVID-19 pandemic, studies have shown that diabetes (type 1 and type 2) is one of the major comorbidities associated with the development of severe COVID-19-related adverse outcomes and mortality (1–8). Adults living with diabetes who contract COVID-19 are at higher risk of developing adult respiratory distress syndrome (ARDS), pneumonia, excessive uncontrolled inflammation responses, and hypercoagulable state (1,6,9). Canadian data—as reported by the Public Health Agency of Canada in September 2020—is consistent with data from other countries in identifying people with diabetes as being hospitalized with more severe disease (13).

Early reports placed the odds of in-hospital death from COVID-19 to be 2.85 times higher in adults living with diabetes compared to patients without diabetes (5). Two recent comprehensive systematic reviews, each reporting on more than 18,000 patients reported an increased risk of death for people living with diabetes (10,11). Chamorro-Pareja et al reported that people with diabetes were 65% more likely to die of COVID-19 in hospital (10). Silverio and colleagues reported a significant and independent association between diabetes and in-hospital mortality after controlling for other risk factors (11). A UK report of 10,926 COVID-19-related deaths, showed that people with diabetes with an A1C measurement greater than 7.5% within the previous 15 months had an increased rate of mortality compared to people without diabetes (12). Canadian mortality data for deaths due to COVID-19 in 2020 described diabetes as one of the highest frequency comorbidities (14). Pre-existing diabetes was present in more than 12% of these deaths, even in younger adults. The report highlights “the elevated risk facing younger populations with underlying conditions.” Sixty-five percent of people who died from COVID-19 in 2020 had two comorbidities, while 46% had three or more.

Children with diabetes—most often, type 1 diabetes—are not at increased risk of developing COVID-19, and if they do contract the virus, their illness is milder than adults with diabetes (15).

Recently, a new hypothesis has emerged, which postulates a bidirectional relationship between diabetes and COVID-19, such that not only does the presence of diabetes increase the likelihood of developing COVID-19 complications, but that the virus may prompt the development of diabetes. This association is discussed below.

The detection of new-onset diabetes in COVID-19 patients could be a case of undiagnosed prediabetes, diabetes, or pre-existing hyperglycemia (16–20). For instance, certain population groups who do not routinely access health-care services, including those living in northern, remote, and rural regions, may be diagnosed with diabetes as they receive in-hospital COVID-19 testing and



treatment (16). This limited access to routine health-care services adversely affects their diabetes trajectory and related health outcomes. This topic is beyond the scope of this review.

It has been suggested that, in the midst of intensive care units experiencing a surge of challenging COVID-19 cases, overtaxed clinicians may be misdiagnosing the combination of respiratory acidosis and ketosis as diabetic ketoacidosis (21). In essence, COVID-19 may be masking other acute diseases: “clinicians must be aware of other acute diseases that can be veiled by COVID-19 symptoms” (19). Conversely, it has been suggested that clinicians without a heightened sensitivity for the presence of diabetes may not be measuring blood glucose or checking for ketones in new admissions (22). Messler et al propose that blood glucose should be adopted as the fifth vital sign, with or without a COVID diagnosis (after body temperature, pulse, respiration rate, and blood pressure) (23). Checking blood glucose and A1C in patients has been recommended, both to treat hyperglycemia and to avoid missing new diabetes diagnoses (24). Despite these reports, it is important to remember that the small sample sizes in these studies—ranging from a case study of one to four—may not imply causation. (17,25).

The relationship between diabetes and COVID-19 is one that can best be described as a complex pathophysiology that is still not well understood. It has been described as “a classic example of a lethal intersection between a communicable and a non-communicable disease” (26). These early studies show that individuals at high risk of metabolic dysfunction appear at higher risk for complications (27). Individuals with newly-diagnosed diabetes or hyperglycemia at admission experience poorer outcomes in the COVID-19 disease progression than both patients with pre-existing diabetes and those without diabetes (18,28,29).

The Proposed Mechanism of Interaction

A series of news articles published early in the pandemic have discussed the possibility of COVID-19 triggering diabetes in previously healthy people (30–34). The evidence reported in these news articles is largely anecdotal, based on clinical opinion, and a handful of cases (30–34). But diabetes researchers and clinicians acknowledge that the evidence needs to be addressed in a systematic fashion.

Type 1 Diabetes and COVID-19

Are diagnoses of pediatric type 1 diabetes being delayed due to the pandemic? Calls from health-care professionals to avoid non-urgent in-person visits were intended to curb the spread of COVID-19. Several authors have speculated that this reduction in non-COVID medical care resulted in the unintended consequence of delayed presentation of pediatric disease, preventing timely diagnosis and treatment and increasing the severity of DKA upon presentation (9,35–37).



Is the virus unmasking or triggering type 1 diabetes? There have been factors hypothesized to influence development of type 1 diabetes, including psychological stress, exposure to the coronavirus, or delayed presentation (35,38–40). In a review of cases across 217 German pediatric diabetes centres, Tittel et al reported no significant increase in new cases of type 1 diabetes due to the pandemic lockdown, compared to the previous nine years (38). There have been reports of new-onset type 1 diabetes, with authors speculating that exposure to the novel coronavirus is at play in these handful of cases (40). Longer-term research is planned to ascertain this potential link.

Genetic (predisposition to a disease) and non-genetic (e.g., environmental) factors interact in the development of type 1 diabetes (41). Previous research on non-genetic mechanisms that contribute to the development of type 1 diabetes have reported the presence of viral infections prior to diabetes diagnosis (41–46). This includes enteroviral infections, which are the most common group of viruses in the world (47), as well as respiratory viruses (48). In a study of co-infection between COVID-19 and other respiratory illnesses, enteroviruses/rhinoviruses were reported as the most common co-infection (6.9%), followed by respiratory syncytial virus (5.2%) (48). In an examination of diabetes and pandemic influenza, a large cohort study in Norway reported an increased incidence of type 1 diabetes for individuals with laboratory-confirmed influenza. (42). But, like COVID-19 and its link to type 1 diabetes, the authors conclude that it is unclear if the flu caused patients to develop type 1 diabetes or simply accelerated its development. Several more recent publications postulate that SARS-CoV-2, the virus that causes COVID-19, accelerated the development of type 1 diabetes (19,40). It is important to note, though, that viral infections impacting development of type 1 diabetes are reported to precede actual diagnosis by months to even years (9,49). Therefore, new cases of type 1 diabetes, seemingly caused by COVID-19, are more likely due to earlier viral infections or other factors (9).

Like SARS, the first novel coronavirus that caused a global outbreak in 2003, SARS-CoV-2 attacks multiple organs in the body, including the pancreas (6,39,50,51). The earlier study found the SARS coronavirus receptor, angiotensin converting enzyme 2 (ACE2), in the endocrine tissues of the pancreas, resulting in damage to islet cells (the insulin-producing area), leading to acute diabetes and hyperglycemia (51). The authors noted that most of the cases of diabetes that arose during hospitalization disappeared within three years. Another study, in fact, reported that the “transient insulin-dependent diabetes” resolved when the SARS infection improved in patients (52). This concept of coronavirus-induced type 1 diabetes lacking permanence will also be investigated in the case of COVID-19 (33).

A recent comprehensive review of the evidence noted, “there does not yet appear to be compelling epidemiological evidence supporting a population-based increase in the development of T1D in individuals with COVID-19. Although new cases of T1D draw understandable attention during the pandemic, the worldwide annual incidence of T1D ranges from 10-30/100,000, hence tracking



potential changes in COVID-19-associated incidence rates will require careful ascertainment and may be challenging” (53).

Type 2 Diabetes and COVID-19

Is the viral infection with COVID-19 causing stress hyperglycemia? During acute illness, the body's protective defenses can induce stress hyperglycemia, a condition consisting of hyperglycemia, insulin resistance, and glucose intolerance (24,54). In addition to being severely ill with COVID-19, hospitalized patients may experience further stress on their bodies as a result of intubation and other treatments such as glucocorticoids (16). In fact, stress hyperglycemia is commonly seen in patients being treated in intensive care units (55). Many of these cases of stress hyperglycemia resolve as patients recover and are discharged from hospital (16). Multiple studies have reported that patients with admission hyperglycemia and no known diabetes fared worse than patients with previously diagnosed diabetes and patients with normoglycemia, both in terms of severity of illness and mortality rates (56–58) This phenomenon—admission hyperglycemia with no pre-existing diabetes and its impact on mortality—has been reported in other acute care situations, such as heart failure (59). In fact, Coppelli et al postulated that the bidirectional relationship is more likely between COVID-19 and stress hyperglycemia (i.e., not diabetes) (58). One study reported that the diabetogenic effect of COVID-19 and the corresponding high insulin requirements for critically ill patients is higher than critical illness caused by other conditions (26). As such, it has been recommended that COVID-19 patients be screened for hyperglycemia upon admission, as well as glycemic control even without pre-existing diabetes (56,60,61). Checking A1C levels upon admission can also assist in identifying patients with newly diagnosed diabetes (62).

Is the virus provoking a severe form of insulin resistance in type 2 diabetes? During episodes of severe illness, patients can develop insulin resistance as a component of stress hyperglycemia (54). The bidirectional relationship of COVID-19 and diabetes may be related to inflammation, as it is present in both conditions: “Chronic diseases [like diabetes] share several standard features with infectious disorders, such as the proinflammatory state, and the attenuation of the innate immune response” (2). Inflammation in the liver causes insulin resistance, which can lead to the development of type 2 diabetes (63). COVID-19 patients with pre-existing diabetes are reported to be “at higher risk of excessive uncontrolled inflammation responses and hypercoagulable state, which may contribute to a poorer prognosis of COVID-19” (6). Indeed, SARS-CoV-2 impacts pancreatic beta-cells, reducing insulin secretion (55). Combined with a hyperactive immune reaction known as “cytokine storm”, which prompts insulin resistance, the virus can become a trigger for stress hyperglycemia and DKA (18,55,64,65). One of the cytokine proteins, interleukin-6, was reported as being present in both DKA and COVID-19 (21,65).

Further, we must acknowledge the way in which the virus enters the body, via ACE2 receptors (6). COVID-19 affects many organs, including the lungs, gut, liver, heart, and pancreas (39,50). These



ACE2 receptors are located in many organs and tissues, including those involved in glucose metabolism: pancreas, small intestine, fat tissues, liver, and kidney (6). It has been hypothesized that the entry of the virus into these tissues is precipitating complex dysfunctions of glucose metabolism (50). Impairing insulin secretion provokes both hyperglycemia and DKA (27).

Are there confounding factors that are masking the true relationship? We must also address the potential role of confounding factors in the reports of new-onset diabetes and hyperglycemia. First, one of the predominant treatments for COVID-19 is the use of glucocorticoids, a class of steroid hormones. This treatment can cause significant variation in blood glucose, and may cause a form of steroid-induced hyperglycemia (66,67). This phenomenon was also observed during the SARS epidemic (37). Second, we must acknowledge the role obesity plays as a potential comorbidity of COVID-induced new-onset diabetes (17), as well as poor outcomes for people with diabetes (20). Obesity complicates an individual's glucose metabolism (20,52), and hyperglycemia is strongly associated with obesity, irrespective of diabetes (68). In fact, some reported case studies registered obesity in the patient profiles, while others noted that missing body-mass index data did not allow obesity to be ruled out as a confounding factor (17,18,25). A systematic review of 75 studies reported that obesity increased people's risk of contracting COVID-19, hospitalization, admission to ICU, and death (68). More data are emerging on the role obesity plays in disease severity and mortality (53,69,70). A comprehensive review of the link between diabetes, obesity, and cardiovascular risk factors to COVID-19 severity and mortality describes it thusly: "Collectively, the available data suggest that the relationship between increasing BMI, severity of SARS-CoV-2 infection and outcomes is not always linear, more relevant in younger people, including children, and frequently complicated in adults by coexisting cardiometabolic risk factors" (53).

Further, lockdown measures in various countries resulted in reduced physical activity, unhealthy eating, and weight gain (71). Taken together, these lifestyle changes can advance insulin resistance, trigger inflammatory pathways, and increase the potential for new-onset diabetes in high risk individuals (72).

Summary

While this new hypothesis linking COVID-19 to the development of diabetes is worthy of discussion, extensive research is needed to distinguish whether there is a causal relationship. Future research needs to include "well-constructed epidemiological cohort studies and mechanistic and experimental studies" (33).

Crucial first steps toward teasing out the true nature of this bidirectional relationship have begun. The first study comparing new-onset diabetes during the pandemic to cases of newly diagnosed diabetes before COVID-19 reported no significant difference in symptomatology, phenotype, and C-peptide levels (73). The only difference of note was more severe hyperglycemia in people diagnosed



during the pandemic, which, the authors postulate, could easily be attributed to delayed diagnosis, a change in dietary and exercise patterns due to lockdown measures, or a combination of both. A systematic review examining new-onset diabetes in COVID-19 patients reported a 14% rate among 3,711 hospitalized patients across eight studies (26). But this result does not confer causation, and the authors note that, “the true proportion is unknown as all studies were hospital-based, and the patients were mostly severely or critically ill” (26).

Currently, an international group of leading diabetes researchers, from King’s College London and Monash University, are in the process of establishing a Global Registry of COVID-19-related diabetes, the [CoviDiab Registry](#) (74). The goal of the registry is to understand the expression of diabetes in patients with COVID-19, and to establish the best approach for treatment and monitoring of affected patients. The authors postulate that COVID-19 has multiple effects on glucose metabolism that need to be understood. The registry will investigate the nature of this bidirectional relationship on several fronts:

- The presence of COVID-19 and high blood glucose with no history of diabetes or problems controlling blood glucose.
- The possibility that COVID-19 induces the development of either type 1 diabetes, type 2 diabetes, or a new, as yet unidentified, type of diabetes.
- The permanence of newly diagnosed type 1 diabetes in COVID-19 patients.
- The possibility that COVID-19 accelerated development of type 2 diabetes in patients who were already on their way to developing it.

In Canada, clinicians and researchers should also seek to explore the characteristics and etiology of new-onset, COVID-19-related diabetes, by establishing their own registries or by contributing patient data to established registries. Diabetes Canada will continue to monitor the research and provide updates and interpretation of this complex, ever-evolving situation.

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