



Relationship between Diabetes and COVID-19 July 2020 – updated Sept 2020

Since the beginning of the COVID-19 pandemic, studies have shown that diabetes is one of the major comorbidities associated with the development of severe COVID-19-related adverse outcomes and mortality (1–6). People 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). Further, the odds of in-hospital death from COVID-19 has been found to be 2.85 times higher in people living with diabetes compared to patients without diabetes (5).

Recently, a new hypothesis has emerged, which indicates that there may be a bidirectional relationship between diabetes and COVID-19, in that not only does the presence of diabetes impact developing COVID-19 complications but the COVID-19 virus may impact the development of diabetes. We must address the possibility that the relationship is, in fact, not bidirectional.

The detection of diabetes in COVID-19 patients could be a case of undiagnosed prediabetes, diabetes, or pre-existing hyperglycemia (7–10). 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 (7). It is a potential situation that highlights the impact of lack of access to routine health-care services experienced by certain population groups, which in turn adversely affects their diabetes trajectory and related health outcomes, a topic that is beyond the scope of this review.

Additionally, 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 (11). 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” (10). Finally, the small sample sizes being reported in these studies—ranging from a case study of one to three or four—could simply reflect sampling bias (8).

The relationship between diabetes and COVID-19 is one that can best be described as a complex pathophysiology that is still not well understood. These early studies show that individuals at high risk of metabolic dysfunction are at higher risk for complications (12). In two studies, individuals with newly-diagnosed diabetes or hyperglycemia at admission experienced poorer outcomes in the COVID-19 disease progression than both patients with pre-existing diabetes and without diabetes (9,13).



The Proposed Mechanism of Interaction

Emerging evidence suggests that COVID-19 may have a specific impact on the development of diabetes, as well as diabetes-related metabolic conditions such as diabetic ketoacidosis (DKA) and hyperosmolar syndrome (14). Most often linked to type 1 diabetes, DKA is an urgent complication that is the result of insulin deficiency resulting in excess ketones (acids created when fat is broken down to be used for energy). Hyperosmolar syndrome, most often seen in type 2 diabetes, is an equally urgent complication, involving extremely high blood sugar levels without the presence of ketones.

A series of news articles published earlier this year (June 2020) have discussed the possibility of COVID-19 triggering diabetes in previously healthy people (15–19). The evidence reported in these news articles is largely anecdotal, based on clinical opinion, and a handful of cases (15–19). But diabetes researchers and clinicians acknowledge that the evidence needs to be addressed in a systematic fashion.

A letter to the editor published in *The New England Journal of Medicine* by Rubino et al., discussed the bidirectional relationship between COVID-19 and diabetes (20). The authors suggested that it is possible that COVID-19 could cause “pleiotropic alterations of glucose metabolism that could complicate the pathophysiology of pre-existing diabetes or lead to new mechanisms of disease” (20). The nature of this relationship warrants further examination. We break down the reported evidence into possible scenarios below.

Type 1 Diabetes and COVID-19

A letter to the editor published in *Diabetes Research and Clinical Practice* by Chee et al., reported a “case of DKA precipitated by COVID-19 in a patient with newly diagnosed diabetes mellitus” (14). The authors concluded that it is possible that COVID-19 could aggravate pancreatic beta cell function and accelerate the development of DKA (14).

Is the virus unmasking or triggering type 1 diabetes? Genetic (predisposition to a disease) and non-genetic (e.g., environmental) factors interact in the development of type 1 diabetes (21). 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 (21–25). This includes enteroviral infections, which are the most common group of viruses in the world (26), as well as respiratory viruses (27). Interestingly, 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%) (27). 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. (22). 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 (10,28).

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 (6,20,29,30). 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 (29). 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 (31). This concept of coronavirus-induced type 1 diabetes lacking permanence will also be investigated in the case of COVID-19 (18).

Type 2 Diabetes and COVID-19

Is the virus 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 (32). 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 (7). In fact, stress hyperglycemia is commonly seen in patients being treated in intensive care units (33). Many of these cases of stress hyperglycemia resolve as patients recover and are discharged from hospital (7).

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 (32). 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 (34). 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 (33). Combined with a hyperactive immune reaction known as “cytokines storm”, which prompts insulin resistance, the virus can become a trigger for stress hyperglycemia and DKA (9,33,35,36). One of the cytokine proteins, interleukin-6, was reported as being present in both DKA and COVID-19 (11,36). 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 (20,30). Indeed 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 (20). Impairing insulin secretion provokes both hyperglycemia and DKA (12).



More Evidence is Required

While this new hypothesis linking COVID-19 to the development of diabetes is worthy of discussion, extensive research is needed to distinguish whether this relationship truly exists, and if it is a case of correlation or causation. Future research needs to include “well-constructed epidemiological cohort studies and mechanistic and experimental studies” (18). 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 in fact cause significant variation in blood glucose, and may cause a form of steroid-induced hyperglycemia (37,38). 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 (8). Obesity complicates an individual’s glucose metabolism (31). 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 (8,9).

Crucial first steps toward teasing out the true nature of this bidirectional relationship have begun. Currently, an international group of leading diabetes researchers, out of the King’s College London and Monash University, are in the process of establishing a Global Registry of COVID-19-related diabetes, the [CoviDiab Registry](#) (39). 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:

1. The presence of COVID-19 and high blood glucose with no history of diabetes or problems controlling blood glucose.
2. 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.
3. The permanence of newly diagnosed type 1 diabetes in COVID-19 patients.
4. 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.



References

1. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol*. 2020 Jun;8(6):546–50.
2. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis*. 2020 May;94:91–5.
3. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. *Arch Acad Emerg Med [Internet]*. 2020 Mar 24 [cited 2020 Jul 2];8(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7096724/>
4. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020 Mar 11;1–8.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*. 2020 Mar 28;395(10229):1054–62.
6. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev [Internet]*. 2020 Apr 7 [cited 2020 Jul 2]; Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7228407/>
7. Vieira G. Is COVID-19 Triggering Type 1 and Type 2 Diabetes? [Internet]. Healthline. 2020 [cited 2020 Jul 2]. Available from: <https://www.healthline.com/health-news/is-covid-19-triggering-type-1-and-type-2-diabetes>
8. Suwanwongse K, Shabarek N. Newly diagnosed diabetes mellitus, DKA and COVID-19: causality or coincidence? - A report of 3 cases. *J Med Virol [Internet]*. 2020 Jul 24 [cited 2020 Sep 16]; Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7404645/>
9. Fadini GP, Morieri ML, Boscaro F, Fioretto P, Maran A, Busetto L, et al. Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by aggravating respiratory deterioration. *Diabetes Res Clin Pract*. 2020 Oct;168:108374.
10. Potier L, Julla JB, Roussel R, Boudou P, Gauthier DC, Ketfi C, et al. COVID-19 symptoms masking inaugural ketoacidosis of type 1 diabetes. *Diabetes Metab [Internet]*. 2020 May 21 [cited 2020 Sep 16]; Available from: <http://www.sciencedirect.com/science/article/pii/S1262363620300811>



11. Gentile S, Strollo F, Mambro A, Ceriello A. COVID-19, ketoacidosis and new-onset diabetes: Are there possible cause and effect relationships among them? *Diabetes Obes Metab*. 2020 Aug 13;
12. Endocrinology TLD&. COVID-19 and diabetes: a co-conspiracy? *Lancet Diabetes Endocrinol*. 2020 Oct 1;8(10):801.
13. Singh AK, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. *Diabetes Res Clin Pract* [Internet]. 2020 Aug 25 [cited 2020 Sep 16]; Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7445123/>
14. Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res Clin Pract*. 2020 Jun;164:108166.
15. Hamilton-Shield J. Coronavirus could trigger diabetes in previously healthy people [Internet]. *The Conversation*. [cited 2020 Jul 2]. Available from: <http://theconversation.com/coronavirus-could-trigger-diabetes-in-previously-healthy-people-140886>
16. Campanile C. Diabetes appears in patients with rare coronavirus-linked Kawasaki disease [Internet]. *New York Post*. 2020 [cited 2020 Jul 2]. Available from: <https://nypost.com/2020/05/11/diabetes-appears-in-patients-with-coronavirus-linked-kawasaki-disease/>
17. Is COVID-19 Triggering Type 1 and Type 2 Diabetes? [Internet]. *Healthline*. 2020 [cited 2020 Jul 2]. Available from: <https://www.healthline.com/health-news/is-covid-19-triggering-type-1-and-type-2-diabetes>
18. COVID-19 may trigger new diabetes, experts warn [Internet]. *ScienceDaily*. [cited 2020 Jul 2]. Available from: <https://www.sciencedaily.com/releases/2020/06/200612172220.htm>
19. Mallapaty S. Mounting clues suggest the coronavirus might trigger diabetes. *Nature*. 2020 Jun 24;583(7814):16–7.
20. Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. New-Onset Diabetes in Covid-19. *N Engl J Med*. 2020 Jun 12;0(0):null.
21. Jerram ST, Dang MN, Leslie RD. The Role of Epigenetics in Type 1 Diabetes. *Curr Diab Rep* [Internet]. 2017 [cited 2020 Jul 2];17(10). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5559569/>
22. Ruiz PLD, Tapia G, Bakken IJ, Håberg SE, Hungnes O, Gulseth HL, et al. Pandemic influenza and subsequent risk of type 1 diabetes: a nationwide cohort study. *Diabetologia*. 2018;61(9):1996–2004.



23. Stene LC, Rewers M. Immunology in the clinic review series; focus on type 1 diabetes and viruses: the enterovirus link to type 1 diabetes: critical review of human studies. *Clin Exp Immunol*. 2012 Apr;168(1):12–23.
24. Coppieters KT, Wiberg A, Tracy SM, von Herrath MG. Immunology in the clinic review series: focus on type 1 diabetes and viruses: the role of viruses in type 1 diabetes: a difficult dilemma. *Clin Exp Immunol*. 2012 Apr;168(1):5–11.
25. Krogvold L, Edwin B, Buanes T, Frisk G, Skog O, Anagandula M, et al. Detection of a Low-Grade Enteroviral Infection in the Islets of Langerhans of Living Patients Newly Diagnosed With Type 1 Diabetes. *Diabetes*. 2015 May 1;64(5):1682–7.
26. Factsheet about enteroviruses [Internet]. European Centre for Disease Prevention and Control. [cited 2020 Jul 2]. Available from: <https://www.ecdc.europa.eu/en/enteroviruses/facts>
27. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. *JAMA*. 2020 May 26;323(20):2085–6.
28. Unsworth R, Wallace S, Oliver NS, Yeung S, Kshirsagar A, Naidu H, et al. New-Onset Type 1 Diabetes in Children During COVID-19: Multicenter Regional Findings in the U.K. *Diabetes Care* [Internet]. 2020 Aug 13 [cited 2020 Aug 18]; Available from: <https://care.diabetesjournals.org/content/early/2020/08/13/dc20-1551>
29. Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol*. 2010;47(3):193–9.
30. Yang L, Han Y, Nilsson-Payant BE, Gupta V, Wang P, Duan X, et al. A Human Pluripotent Stem Cell-based Platform to Study SARS-CoV-2 Tropism and Model Virus Infection in Human Cells and Organoids. *Cell Stem Cell*. 2020 Jul;27(1):125–136.e7.
31. Smith SM, Boppana A, Traupman JA, Unson E, Maddock DA, Chao K, et al. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. *J Med Virol* [Internet]. [cited 2020 Sep 16];n/a(n/a). Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.26227>
32. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care*. 2013;17(2):305.
33. Ceriello A. Hyperglycemia and COVID-19: What was known and what is really new? *Diabetes Res Clin Pract* [Internet]. 2020 Aug 25 [cited 2020 Sep 16]; Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7445137/>



34. Asrih M, Jornayvaz FR. Inflammation as a potential link between nonalcoholic fatty liver disease and insulin resistance. *J Endocrinol*. 2013 Sep;218(3):R25-36.
35. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the Eye of the Cytokine Storm. *Microbiol Mol Biol Rev MMBR*. 2012 Mar;76(1):16–32.
36. Reddy PK, Kuchay MS, Mehta Y, Mishra SK. Diabetic ketoacidosis precipitated by COVID-19: A report of two cases and review of literature. *Diabetes Metab Syndr*. 2020;14(5):1459–62.
37. Li G. Inpatient use of glucocorticoids may mediate the detrimental effect of new-onset hyperglycemia on COVID-19 severity. *Diabetes Res Clin Pract* [Internet]. 2020 Sep 11 [cited 2020 Sep 16];0(0). Available from: [https://www.diabetesresearchclinicalpractice.com/article/S0168-8227\(20\)30694-X/abstract](https://www.diabetesresearchclinicalpractice.com/article/S0168-8227(20)30694-X/abstract)
38. Sitepu AN, Syafril S. Case Report: A Confirmed COVID-19 Patient with Type 2 Diabetes Mellitus | *Journal of Endocrinology, Tropical Medicine, and Infectious Disease (JETROMI)*. *J Endocrinol Trop Med Infect Dis*. 2020;2(3):144–52.
39. CoviDiab Registry [Internet]. [cited 2020 Jul 2]. Available from: <https://covidiab.e-dendrite.com/>