



Increased Risk of Diabetes and Diabetic Ketoacidosis Associated With COVID-19

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It is known that pancreatic β -cells are permissive to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection through the expression of ACE receptor 2 (1) and that the infection may also induce indirect β -cell damage through a cytokine storm and a proinflammatory milieu (2). It has also been shown that inflammatory and immunological alterations (3) following a coronavirus disease 2019 (COVID-19) infection may lead to acute and long-term disruption of glucose metabolism (4–6). A recent study showed that the combination of augmented circulating inflammatory factors that exert toxic effects on human pancreatic islets and SARS-CoV-2-specific viral RNA in pancreatic tissues, together with the alteration of secretory granules, promotes glucose metabolism alterations (7). Despite the increasing number of observations, the complex pathogenic model that links COVID-19 and new-onset diabetes has not been fully clarified yet. Many retrospective studies, systematic reviews, and meta-analyses reported an increase in new-onset diabetes associated with COVID-19 (8). A recent meta-analysis by Banerjee et al. (9) showed 59% higher risk of individuals developing diabetes in the postacute COVID-19 phase versus the risk for healthy control individuals (hazard ratio [HR] 1.59) and versus the risk for severity-matched non-COVID-19 respiratory tract infections (moderate-severe/hospitalized cases, HR 1.52; mild cases, HR 1.22), while a role for steroid use was excluded (steroids vs. no steroids, relative risk 1.42 vs. 1.46). Epidemiological observations on new-onset type 1 diabetes are showing even more contrasting results. A possible delay in the diagnosis or the reduced accessibility of health care services during the pandemic period may have also played a role in the increase in diabetic ketoacidosis diagnosis (10). The epidemiological impact of COVID-19 infection on the incidence of type 1 and type 2 new-onset diabetes in the real world has not been established yet due to the lack of prospective studies and of adequate control populations in the published studies.

The study by Sharma et al. (11) showed association between SARS-CoV-2 infection and the derangement of glucose metabolism through analysis of a large cohort of patients with COVID-19 infection compared with a large matched cohort of patients without COVID-19 infection. The authors also evaluated HbA_{1c} levels longitudinally pre- and post-infection. Finally, the authors explored the occurrence of diabetic ketoacidosis, excluding patients with previous diabetic ketoacidosis history and those who received a diagnosis of hyperosmolar hyperglycemic syndrome. The authors obtained data on new-onset diabetes after COVID-19 infection in a real-world cohort, but they also conducted a case-control study on diabetes-related complications of COVID-19 infection. This study has some limitations. Among those, we should mention that a selection bias should not be excluded due to the selection of only patients whose data are in a clinic registry. Moreover, authors included only patients who had HbA_{1c} measurement in the 12 months before the COVID-19 test, but many data on HbA_{1c} values are lacking, and it is possible that this contributed to an additional selection bias in the groups of patients with COVID-19 and without COVID-19. Thus, the reproducibility of data obtained from this specific population is uncertain. Indeed, it is possible that patients with risk factors for diabetes may be enrolled. Second, the authors did not evaluate the impact of hypoglycemic drugs on HbA_{1c} changes in the subgroups of patients with type 1 and type 2 diabetes, thus is not possible to exclude different changes in intensity of care, especially in the COVID-19 group.

Newly published data confirm the negative impact of COVID-19 on glycometabolic control, leading to higher rates of diabetes diagnosis in infected subjects and to the worsening of glucose control in those patients already diagnosed with diabetes with a higher rate of diabetic ketoacidosis (11). Some aspects should still be clarified. For

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instance, mechanisms of the deleterious link between COVID-19, diabetes, and diabetes risk factors for this manifestation after COVID-19 infection are not known. Moreover, the mechanisms with which infection could trigger ketoacidosis have not been explored yet, and it is not clear if COVID-19 infection disrupts immune tolerance. Undoubtedly, better phenotyping of patients with COVID-19 infection and validated outcome measures of glucose metabolism or insulin resistance status following infection are needed for deeper knowledge of the subject.

In conclusion, SARS-CoV-2 infection has a role in facilitating or promoting the complex pathogenesis of new-onset diabetes and in the derangement of glycometabolic control in those patients who have already been diagnosed with diabetes. However, many questions remain unsolved. Indeed, it probably would be advisable to conceive surveillance strategies to better protect exposed patients and to deeply understand the burden of the problem.

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