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Editorial

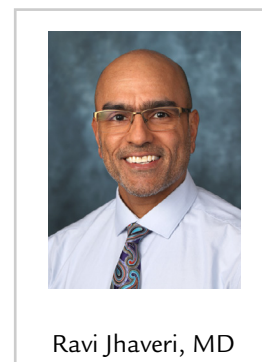
How COVID-19 Is Helping Us Learn More About Diabetes Pathogenesis

In this month's Topic Update, we present a collection of articles on various aspects of diabetes mellitus (DM). The authors discuss novel treatments for patients with nonalcoholic fatty liver disease and the promise of candidate biomarkers for both diabetic neuropathy and nonalcoholic fatty liver disease. We thank Topic Editor Uazman Alam and all of the contributing authors for sharing their expertise. This issue comes at the same time as yet another resurgence of COVID-19 in the United States and elsewhere around the world. Driven by the increased transmissibility of the delta variant, the ongoing infections remind us that our continued vigilance is needed for the foreseeable future.^{1,2}

I want to take a moment to tie together the topics of DM and COVID-19. Early in the pandemic, DM was associated with increased COVID-19-related mortality and severity of disease.³ Since that time, some fascinating studies have been focused on the impact of COVID-19 on those with DM. Rather than being specific to this infectious disease, these studies highlight some of the common ways that different infections are linked with DM.

A consistent observation in the first few months of the initial surge of COVID-19 cases was the description of poorer outcomes in diabetic patients, who were overrepresented among patients who required hospitalization and subsequent intensive care unit admission.⁴ Also interesting was the rate of diabetic ketoacidosis (DKA) associated with COVID-19.⁵ The T1D Exchange Quality Improvement Collaborative conducted a US-based study in patients with type 1 DM who presented with COVID-19. In their analysis, they found that more than half of patients were hyperglycemic when they presented with COVID-19, and almost one third were diagnosed with DKA. A subsequent study further described a very high rate of DKA among patients with type 2 DM when they developed COVID-19, compared to the rate in patients with type 1 DM, in whom DKA is usually more common.⁶ These patients had poor glucose control on admission and ultimately had poorer outcomes with COVID-19, with higher rates of vasopressor use, need for mechanical ventilation, and mortality. While infection and DKA were frequently associated in patients with pneumonia or urinary tract infection, the rates observed in patients with COVID-19 seemed to far exceed the rates in patients with other infections.⁷ What factors of SARS-CoV-2 might explain this difference?

The authors of two articles published last spring evaluated the direct impact of SARS-CoV-2 infection on pancreatic β cells. The first study demonstrated that pancreatic β cells express the entry factors for SARS-CoV-2 infection, and subsequently used elegant fluorescence microscopy to document *ex vivo* SARS-CoV-2 infection of isolated pancreatic β cells from deceased donors.⁸ To demonstrate the direct clinical relevance, they then isolated tissue from patients who died after severe COVID-19 to demonstrate SARS-CoV-2 protein and RNA within pancreatic β cells. To provide functional evidence of the link to DM, the authors documented that SARS-CoV-2 infection of pancreatic β cells led to decreased insulin secretion and apoptosis. The second study used single-cell RNA sequencing methods to replicate the findings of SARS-CoV-2 infection of pancreatic β cells.⁹ They went on to show that SARS-CoV-2 infection of pancreatic β cells led to the expression of chemokines and other cell-stress markers, and eventually led to cellular transdifferentiation. In other words, SARS-CoV-2 infection of pancreatic β cells made them transition from their initial insulin-secreting phenotype to a phenotype of increased glucagon and trypsin secretion that would be more characteristic of a pancreatic α cell. It is important to emphasize that prior studies have demonstrated that the activation of the downstream cellular pathways was associated with pancreatic β -cell dedifferentiation, so this could happen with any virus that activates these pathways and is not specific to SARS-CoV-2.¹⁰ Not only do the findings of reduced insulin secretion support the increased cases of DKA, but also the overall body of work supports the long-held hypothesis that viral infections are a key inciting event of type 1 DM that drives the autoimmune destruction of pancreatic β cells.¹¹



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With an estimated 2019 global prevalence of almost 500 million people, DM has evolved into one of the world's greatest health threats.¹² Superimposed on a global pandemic with many highly populous countries with woefully inadequate vaccination rates, the unique synergy of SARS-CoV-2 infection with DM will continue to drive severe morbidity and mortality for the duration.¹³ We can only hope that some of the biomarkers and new therapies discussed by our guest authors in this Topic Update help to improve outcomes in these patients sooner rather than later. In the meantime, please everyone get your vaccines, get your booster doses, wear a mask, and be safe.

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