# COVID-19 and Rising Incidence of Diabetes: Despite Evolving Data, an Enigma Still to Be Solved

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COMMENTARY



Since the start of the coronavirus disease 2019 (COVID-19) pandemic in 2020, the global scientific and medical communities have learned important lessons about this disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As the pandemic unfolded, we were informed about the major risk factors associated with the disease and had a heightened awareness of the disparities given that racial and ethnic minority groups were disproportionately affected (1,2). We witnessed incredible and rapid progress for research advances that led to improved management strategies and development of innovative therapeutics that resulted in significant reduction in morbidity and mortality (3). However, despite the successes, we are continuing to face growing concerns with postacute sequelae of SARS-CoV-2 infection. Specifically, a great concern is the emerging epidemiologic evidence showing increases in the incidence of diabetes in both adults and children following SARS-CoV-2 infection (4–6). Given the increased prevalence and incidence of diabetes that currently exists worldwide and the projections for future years (7), a further increase in global diabetes rates resulting from COVID-19 would be an enormous public health burden. However, despite the reports to date, there remain too many unanswered questions. Thus, this issue of *Diabetes Care* includes three reports that provide new data that continue to inform on this issue (8–10).

In the study from Sasidharan Pillai et al. (8), the authors conducted a retrospective chart review to describe the evolving impact of the COVID-19 pandemic on the incidence and presentation of new-onset pediatric type 2 diabetes. They compared annualized incidence rates from the prepandemic period with the first and second pandemic years for 144 patients who met eligibility criteria. They reported that the annualized incidence of type 2 diabetes increased approximately threefold from prepandemic to pandemic years. BMI percentiles of the patients steadily increased over time and were higher during the pandemic years. They concluded that the increase in BMI percentiles in new-onset type 2 diabetes cases "likely reflects pandemic-related obesogenic factors, including decreased physical activity, poor sleep hygiene, increased screen time, and energy-dense food consumption."

The strength of the study by Sasidharan Pillai et al. (8) lies in the fact that it provides data on incidence and metabolic parameters of youth-onset type 2 diabetes over 2 years of the pandemic. It confirms prior reports on the adverse effect of the pandemic on factors such as BMI that contribute to development of type 2 diabetes in youth (11). The limitations of the study were the retrospective approach to chart review, the paucity of data on current or prior history of COVID-19 infection, and the small number of subjects evaluated. It appeared that even though the number of patients was not large in any one year, based on percentages shown for the cohort of youth with type 2 diabetes, there was a representative percentage of certain racial and ethnic groups.

The study from McKeigue et al. (9) provides a thorough evaluation of the increased incidence of type 1 diabetes in individuals <35 years old in Scotland. Specifically, the authors sought to replicate the findings of Barrett et al. (5) who reported increased incidence of diabetes 30 days or more after SAR-CoV-2 infection in those under 18 years. Given the recent data on new diabetes diagnosis in younger individuals (5) and specifically the increase in type 1 diabetes in pediatric patients (12), the contribution from McKeigue et al. (9) is timely. From a cohort of 1,849,411 individuals aged <35 years without diabetes, including all those in Scotland who subsequently tested positive for SARS-CoV-2, incident type 1 diabetes was ascertained from the national register in Scotland. They reported there were 365,080 individuals who had at least one detected SARS-CoV-2 infection during follow-up and 1,074 who developed type 1 diabetes. In those aged 0–14 years, they observed a 1.2-fold increase in the incidence of type 1 diabetes over

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the study period. However, in a cohort analysis, incident type 1 diabetes was not shown to be associated with SARS-CoV-2 infection, and a causal effect of SARS-CoV-2 was not supported by the data.

There are many strengths to the study from McKeigue et al. (9), including the availability of individual-level data, comprehensive national coverage of PCR tests, the inclusion of data on the level of negative testing around the time of presentation, and validation of the accuracy of dates of diagnosis of type 1 diabetes in the national register against date of first hospitalization. The limitations cited were that the numbers of incident cases of type 1 diabetes in individuals exposed to SARS-CoV-2 infection were relatively small, so for formal modeling of the hazard ratio, the authors had to use broader categories of 0–30 and >30 days for the exposure period.

The third report in this issue of *Diabetes Care* is from Holman et al. (10). The authors outline the rationale for their study by reviewing data suggesting a higher incidence of diabetes following acute illness with COVID-19. They make the case that it is not clear from the data whether the findings of increased incidence of diabetes after COVID-19 reflects shared risk factors, a specific effect resulting from the SARS-CoV-2 virus, or the physiological stress that is observed from an acute infection. They also suggested that we also consider that a period of severe illness requiring intensive care unit admission, regardless of the cause, may be associated with an elevated incidence of type 2 diabetes, as shown in prior studies (13).

The stated aim was "to assess the incidence of diabetes following acute illness with COVID-19 compared with people who had experienced a similar infectious illness by linking national administrative records on hospitalizations to the National Diabetes Audit" (10). They identified incident diabetes after discharge of individuals admitted to the hospital for COVID-19 and/or pneumonia between 1 April 2020 and 30 August 2020 and used comparator cohorts admitted with pneumonia over the same dates in 2017–2019. They demonstrated that compared with people who had been admitted to the hospital with a different acute infection (pneumonia) both in 2020 and in previous years, they were not able to show clear evidence of a higher incidence of diabetes in those hospitalized with COVID-19 compared with risks in their carefully assessed comparator groups.

There are many strengths to the study of Holman et al. (10). The study design and methodologic approach were well conceived, and the use of the population-wide data on hospital admissions for severe COVID-19 linked to the National Diabetes Audit was a strength. The limitations included the fact that the time frame of study may not have been long enough to capture differential risks of developing diabetes following severe illness with COVID-19 and that it was not possible to accurately distinguish between the incidence of type 1 and type 2 diabetes.

Collectively, the three studies in this issue of *Diabetes Care* add to the growing body of evidence that informs on rising incident diabetes cases after COVID-19 and advance the understanding of this complicated issue. However, we are still left with many unanswered questions. Can the reports of rising cases of incident diabetes be fully explained, as outlined by the elegant studies from McKeigue et al. (9) and Holman et al. (10)? Based on the observations of other cited and carefully conducted studies, is the increase real? If real, do the new cases after COVID-19 represent a new form of diabetes? Data to date suggest the human pancreas is a target of SARS-CoV-2, and several postulated mechanisms are proposed to contribute to metabolic dysfunction and increase in diabetes (14–16). Given that the type or characteristics of diabetes after COVID-19 have not been well described, there is still a great need to conduct the deep metabolic, molecular, and clinical phenotyping.

Are the reports of rising cases related to significant stress of acute infection or perhaps, as suggested by Sasidharan Pillai et al. (8), a consequence of pandemic conditions? Are we seeing an increase in cases from the contribution of those individuals who were previously undiagnosed or who had prediabetes? With the myriad of factors related to the pandemic state, are these individuals experiencing an accelerated progression or is the condition simply being unmasked? Is the natural history of these cases similar to that of diabetes onset and progression of the disease observed before the pandemic? Do we really appreciate the effect of increased psychosocial stress during the pandemic and its role in diabetes onset?

We still have a significant amount of work to do to fully understand the reasons behind the reports of increased cases. The fact that we do not have definitive answers yet despite these studies speaks to the complexity of this issue. Further research, including more data on the natural history and in-depth characterization and phenotyping of the diabetes cases, remains a logical progression and next best steps in research to provide further understanding. Thus, with the existing challenge to fully explain the observations of diabetes after COVID-19 infection, it is exciting to realize that we are ushering in a new era that calls for a fresh perspective to address diabetes development.

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