Diabetes and COVID-19: Moving From News to Knowledge and a Glucose Hypothesis

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Science makes civilization possible. New observations provoke theories as to what they mean. Theories (hypotheses) are tested by systematically gathering and analyzing further information. Support for a theory by these methods (experiments) can lead to a plan of action. Other observations from this process (research) may pose further questions, leading to more experiments. In the past, actionable knowledge accumulated slowly, but digital technology has accelerated everything. Novel observations appear as "news" distributed by electronic, broadcast, and print media. Floods of reports, all apparently equal in significance, compete for attention. The media have insatiable appetites—they demand new material daily. Delivery of news is driven by its power to elicit emotional reactions, and we are all somewhat addicted. But news does not teach us what to do. Some items are valid and reproducible, others confusing, some misleading. Each can be placed in context, verified, and converted into useful knowledge using the scientific method, but this takes time.

Experience with the coronavirus disease 2019 (COVID-19) pandemic and its implications for people with diabetes illustrates this process. *Diabetes Care* has welcomed early reports on COVID-19, even when the first data sets were unavoidably limited. Special collections of articles appeared in the July and August issues, but most were available online earlier (1). These and articles published elsewhere confirmed the alarming news that people with diabetes are up to three times more likely than others to become severely ill or die of COVID-19. They showed that older age, obesity, and other medical conditions often associated with diabetes are also associated with increased risk. These reports highlighted the need for people with diabetes to take precautions to avoid infection, but they did not provide much guidance on how to treat these patients if they did fall ill. Articles by expert clinicians, based on the evidence and experience available at the time, have provided helpful but necessarily tentative guidance (2–4).

Studies reported more recently in *Diabetes Care* have tested specific questions about COVID-19 and diabetes, adding further insights. One important question is whether people with type 1 diabetes (T1D) are as vulnerable as those with type 2 diabetes (T2D). A preliminary survey in the U.S. suggested that people with T1D who developed COVID-19 commonly had severe metabolic decompensation, but the study could not determine whether long-term outcomes were affected (5). A group in Belgium found no support for increased risk of hospital admission with COVID-19 in adults with T1D (6), and a report from Boston showed no difference in clinical features among adults with T1D who were hospitalized with COVID-19 as compared with those hospitalized for other reasons (7). More information is needed, but so far risks related to COVID-19 for people with T1D do not seem as increased as they are for people with T2D.

Two articles in the present issue suggest a disruption of care for foot ulcers in people with diabetes during lockdown for COVID-19 compared with experience the year before (8,9). They report an increased risk of amputation and attribute it to impaired access to providers. A Perspective in a previous issue of *Diabetes Care* proposed that this problem might be avoided by active decentralization of care (10).

Four articles in this issue provide additional clues regarding physiologic links between diabetes and COVID-19. A comparison of national databases in the U.S. showed that people diagnosed with the virus, including many who did not require hospitalization, had greater likelihood of having diabetes or chronic lung disease than adults in the general population but lower prevalence of cardiovascular or renal disease (11). This suggests that, although medical conditions that are often complications of diabetes can favor progression of illness, they do not directly alter risk of infection. This observation draws attention to the likelihood that social and economic factors are contributing to the frequency of infection among disadvantaged populations with

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diabetes in the U.S. Another factor potentially favoring progression to severe illness was documented in a study based on computed tomography of adipose tissue (12). The investigators found visceral adipose tissue thickness was greater in people diagnosed with COVID-19 than in those in a control population. After adjustment for age, sex, and BMI, this measurement remained associated with progression to an intensive care unit. Thus, visceral fat accumulation may be a better predictor of risk than obesity alone. Two more mechanistic studies addressed the possible role of the renin-angiotensin system (RAS) based on evidence that angiotensin-converting enzyme 2 (ACE2) is a site of entry of the virus into cells. One demonstrated abnormalities of ACE2 and other RAS proteins in blood in people with T2D, but no change in these proteins following rapid improvement of glycemic control using insulin (13). Another showed increased expression of ACE2 in the liver in older age and in the presence of hepatic steatosis and diabetes, all factors associated with risk of progression to severe illness in COVID-19 (14). These clues support further efforts to determine the role of medications affecting RAS activity in patients with diabetes and COVID-19.

Three more articles are relevant to an exceedingly important question regarding COVID-19 in diabetes: does hyperglycemia play a role in progression to severe illness? Most known risk factors for progression—male sex, older age, obesity, and disorders of the heart, kidney, or lung—are not modifiable at the time of diagnosis. When these factors are included in multivariable models along with diabetes, the excess risk associated with a prior diagnosis of diabetes is attenuated or in some cases no longer present. But what about the role of hyperglycemia—or, more generally, poor metabolic control associated with relative insulin deficiency? Importantly, this *is* a modifiable risk factor.

In this issue, Agarwal et al. (15) report a study of 1,126 people with diabetes who were hospitalized for COVID-19. In this large cohort, age, male sex, and BMI were confirmed as risk factors, but HbA_{1c} values at admission or in the last 3 years were not associated with mortality, with or without adjustment for other clinical characteristics. This observation does not support the possibility of reducing risk of serious illness with COVID-19 through improving glycemic control prior to infection. In contrast, hyperglycemia at the time of admission has been noted previously to be associated with poor outcomes. Coppelli et al. (16) added to this evidence by analyzing data from 271 adults who were hospitalized with COVID-19. This population was divided into people with normal glucose levels at entry ($n = 149$), those with glucose >140 mg/dL (7.8 mmol/L) at the time of admission but without known diabetes ($n = 66$), and those with previously diagnosed diabetes ($n = 56$). Compared with the group with normal glucose, mortality was greater in the hyperglycemic group without diabetes (39% vs. 17%, hazard ratio 2.20 [95% CI 1.27–3.81], $P = 0.005$) and perhaps also in the group with diabetes (29% vs. 17%, hazard ratio 1.73 [0.92–3.25], $P = 0.086$). In a multivariable model of the whole population, hyperglycemia was a strong independent predictor of mortality. These observations suggest that controlling hyperglycemia from the time of hospitalization might reduce progression to severe illness or death, even for people not known to have diabetes previously.

Both indirect and direct evidence supports this hypothesis. Physiologic studies have shown rapid and marked improvement of various inflammatory markers after infusion of insulin in obese people with diabetes (17–19). A small study by Sardu et al. (20) found better outcomes in a group of patients with hyperglycemia at hospitalization for COVID-19 when intravenous insulin was started immediately. However, maintenance of tight control for very ill patients is challenging, especially when glucocorticoids are used. Some patients will need multiple injections, increasing demands upon personnel needing protective equipment. Also, glucose levels must be carefully tracked to guide dosing and protect against hypoglycemia. A prior report of continuous glucose monitoring (CGM) in this setting is relevant to this concern (21). In the present issue, Reutrakul et al. (22) describe using CGM for noncritically ill patients with COVID-19 on hospital wards. Larger studies of in-hospital use of CGM will follow and may facilitate both study and routine use of intravenous insulin as a basis for intensive metabolic control in patients with COVID-19.

This commentary aims to highlight the rapid progress in understanding COVID-19 and its relation to diabetes. *Diabetes Care* strives to maintain high standards in selecting articles on this crucial topic. Like all scientific journals, it cannot compete with broadcast media, data aggregators, or preprint servers in speed of reporting news. Its mission is to present peer-reviewed studies that can be trusted. Even though this process takes time, the links between diabetes and COVID-19 are being clarified quite rapidly, as is reflected by the articles summarized above. An important next step will be testing the hypothesis that immediate restoration of basal insulin sufficiency can improve outcomes for people afflicted with COVID-19. We look forward to seeing the evidence as it appears.

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