COVID-19 in People With Diabetes: Urgently Needed Lessons From Early Reports

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Epidemic infections have frightened and harmed people for millennia. Plague (1) and typhus (2), bacterial infections associated with poor sanitation and high mortality, have devastated populations. Both still reappear intermittently, but they are generally contained with better sanitation and control of rodent and insect vectors along with antibiotics. In contrast, viral epidemics persist. A unique strain of influenza caused a global epidemic (pandemic) in 1918 resulting in millions of deaths (3). Among recent outbreaks of viral infections, several have been caused by coronaviruses (4). One of these, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is now causing a pandemic illness termed coronavirus disease 2019 (COVID-19) that poses unique challenges. This novel coronavirus is readily transmitted from person-to-person, even by those who are infected but without symptoms. In susceptible people it causes severe illness and often death from pulmonary and systemic injuries. At present, we have neither a preventive vaccine nor well-studied pharmacotherapy, although work to develop these is vigorously underway.

Certain groups are more vulnerable to COVID-19, notably older people and those with underlying medical conditions. Because diabetes is one of the conditions associated with high risk, the diabetes community urgently needs to know more about COVID-19 and its effects on people with diabetes.

Between the first appearance of this illness in December 2019 and the time of writing this commentary, several detailed clinical descriptions have been published. Among 44,672 patients in China with infection confirmed by nucleic acid testing up to mid-February (5), most (87%) were between 30 and 79 years old. A large majority (81%) were considered to have mild illness, but in 14% it was judged to be severe and in 5% critical. Of all confirmed cases, 2.3% of patients died. Higher mortality rates were found among those ≥80 years old (14.8%), in those with preexisting cardiovascular disease (10.5%), and in men (2.8%) as compared with women (1.7%). Among people with diabetes the mortality rate was 7.3%, more than three times that of the overall population. Two other conditions that are common in those with diabetes were also associated with higher mortality rates: 10.5% for cardiovascular disease and 6.0% for hypertension. Because mortality rates were not stratified by age, it is not clear how much of the excess risk in people with these conditions was independently related to age.

Another report included clinical data collected up to the end of January for 1,099 patients hospitalized with laboratory-confirmed infection in China (6). By far the most common symptoms on admission were fever and cough, and a majority had radiologic evidence of pulmonary disease. Of all patients hospitalized, 6.1% met the composite primary end point, a requirement for intensive care or mechanical ventilation, or died. The prevalence of diabetes in the whole population was 7.4%, but 27% of those meeting the primary end point had diabetes. The overall mortality rate was 1.4%.

A third Chinese report described the clinical features and outcomes of 191 patients hospitalized with a confirmed diagnosis and complete information regarding outcomes (7). Nearly half had a preexisting illness and 19% a diagnosis

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of diabetes. The overall mortality rate was 28%. Multivariable analysis suggested that older age, early evidence of organ failure, and a D-dimer level >1 μg/L on admission were significant risk factors for in-hospital mortality.

A case in the U.S. was confirmed in January 2020 in Washington State. This 35-year-old man was a local resident who had recently traveled to China (8). Soon after, a case in a long-term care facility was identified, a 73-year-old woman with diabetes, obesity, hypertension, and cardiovascular disease who ultimately succumbed to the infection (9). The disease propagated in residents, visitors, and health care personnel at the facility and later elsewhere in the community. Two series of cases admitted to intensive care units in Washington State with confirmed COVID-19 were reported (10,11). In one, 7 of 21 patients had known diabetes, and at the time of the report 67% of the cohort had died and 24% were still in critical condition (10). In the other, 14 of the 24 patients had diabetes and half of the whole group died during the period of observation (11). Data from the U.S. as a whole are being collected by the Centers for Disease Control and Prevention. As of 28 March, more than 74,000 COVID-19 cases had been confirmed. Within a subgroup of 7,162 patients for whom complete data on underlying health conditions were available, diabetes was not more frequent than reported in the general population. However, among those with COVID-19, diabetes was reported in 6% of those not hospitalized, 24% of those hospitalized but not in intensive care, and 32% of those admitted to an intensive care unit (12).

These previous analyses of populations in China with varying severity of illness and clinical outcomes and early reports from the U.S. offer important insights. The rapid accumulation of cases in the first 3 months after recognition of this viral syndrome testifies to its high transmission rate. The mortality figures verify how dangerous COVID-19 can be, and the demonstration of increased risk in older people and those with diabetes and other comorbidities calls for special attention to these groups.

A group of articles recently accepted by *Diabetes Care* focuses specifically on COVID-19 in people with diabetes (13–19). Shi et al. (13) compared the characteristics and outcomes of individuals with diabetes with those of equal numbers of people without diabetes matched for sex and age. They analyzed data from 153 people with diabetes comprising 9.8% of a Chinese population that was hospitalized between 1 January and 8 March 2020 with confirmed COVID-19. The median age was 64 years and 49% were men. Their duration of symptoms prior to hospitalization did not differ from the comparator group and presenting symptoms were similar, but PaO_2 was lower on admission. In-hospital mortality was 20% compared with 10.5% for those without diabetes. Within the group with diabetes, unadjusted comparisons of initial characteristics of those with diabetes who died and survivors showed many differences, including older age, more frequent history of hypertension or cardiovascular disease, and higher glucose, creatinine, and C-reactive protein levels. Multivariable modeling of data from those with diabetes suggested older age and hypertension were independently associated with mortality.

Two reports examined the association of obesity, an emerging risk factor for severe illness in COVID-19, with outcomes. Cai et al. (14) divided 383 patients hospitalized with confirmed COVID-19 into groups considered to be underweight ($n = 16$), of normal weight ($n = 203$), overweight ($n = 123$), or obese ($n = 41$) according to thresholds for BMI used in Asian populations. Compared with the normal weight subgroup, those who were obese did not differ in age or duration of symptoms but had higher rates of diabetes (7.3% vs. 5.4%) or hypertension (22% vs. 14%). After adjustment for these and other clinical features, progression to severe illness (defined as respiratory rate >30 breaths/min, resting oxygen saturation ≤93%, PaO_2/fraction of inspired oxygen [FiO_2] ≤300 mmHg, or need for intensive care) was more frequent in the obese group than the normal weight group (odds ratio [OR] 3.40 [95% CI 1.40–2.86]). This observation is supported by the findings of Gao et al. (15) in 75 Chinese patients hospitalized with confirmed infection who were considered obese (BMI ≥25 kg/m^2) and were matched with 75 nonobese individuals by age and sex. After adjustment for clinical characteristics including the presence of diabetes, the obese group had threefold greater likelihood (OR 3.00, 95% CI 1.22–7.38) of progressing to severe/critical status. A nearly linear relationship between higher BMI and severe/critical illness was demonstrated in the whole cohort.

Chen et al. (16) studied mortality among people with diabetes compared with those without diabetes and investigated whether the type of prior glucose-lowering therapy was associated with outcomes among people with diabetes. They analyzed data from 904 patients hospitalized with either a laboratory or clinical diagnosis of infection, of whom 15% had diabetes. Mortality rates in those with diabetes were two to three times higher than in those without diabetes. Multivariable analyses within the subgroup with diabetes identified older age and higher C-reactive protein as independent predictors of death. Further analyses suggested that use of insulin was associated with worse outcomes. Whether this was due to effects of insulin itself or to characteristics of the patients for whom it was prescribed is not clear.

Yet another question of interest is whether levels of glycemic control correlate with progression to severe illness. This question was addressed by Sardu et al. (17) in 59 patients hospitalized with confirmed COVID-19, of whom 26 had previously diagnosed diabetes and 33 did not. Some of the patients in each group received intravenous insulin infusion to control hyperglycemia, whereas others did not. In a multivariable analysis with adjustment for clinical risk factors, the risk of progression to severe illness was lower among those given intravenous insulin. The findings of this unrandomized comparison were interpreted as suggesting that insulin infusion may improve outcomes. If the benefits of seeking excellent glycemic control by this means are confirmed, close monitoring of glucose levels will be essential. Success in adapting systems for continuous glucose monitoring to remote surveillance by intensive care unit teams was reported by Shenav-Zaltzman et al. (18) in a small number of patients.

Finally, Rao et al. (19) used Mendelian randomization to assess possible associations of various medical conditions and traits with expression of angiotensin-converting enzyme 2 (ACE2). This molecule may be a site of attachment

of the virus responsible for COVID-19 to cells in the lung and elsewhere. They concluded that "diabetes and related traits may increase ACE2 expression, which may influence susceptibility to infection (or more severe infection)." Such observations—which are clearly provocative but not definitive—pose the possibility that increased ACE2 in diabetes could mediate increased vulnerability. It has been suggested that widely used medicines affecting the renin-angiotensin-aldosterone system may have either harmful or favorable effects on COVID-19 infections (20,21), but no definitive evidence to support either hypothesis is yet available.

There is much here to digest. The data reported in these articles were rapidly collected and analyzed, in most cases under urgent and stressful conditions. Thus, some of the analyses are understandably limited due to missing data, incomplete follow-up, and inability to identify infected but asymptomatic patients. Even so, some points are clear. The consistency of findings in these rapidly published reports is reassuring in terms of scientific validity, but the story unfolding is worrisome. Diabetes has not yet been shown to increase the likelihood of infection, but progression to severe illness is more likely in people with diabetes. The frequency of diabetes among patients requiring intensive care is two to three times higher than in the overall population, and mortality rates in those with diabetes are also higher. Neither the mechanisms underlying the increased risk nor the best interventions to limit it have yet been defined, but the studies in this collection of articles offer important clues. Obesity is a major risk factor for diabetes and appears to be an independent risk factor for severe illness in COVID-19. Rates of severe illness are therefore likely to be especially frequent in regions and populations where both obesity and diabetes are common. Because more severe hyperglycemia accompanies progression to severe pulmonary and systemic illness, better metabolic control with insulin infusion or other means may be protective. Complications of diabetes including renal, cardiac, and peripheral vascular disease can be additive risk factors and call for specific attention. Some circulating markers of systemic inflammation are elevated in severe cases, suggesting possible molecular sites for intervention. Of particular interest is the observation that ACE2 expression is associated with diabetes and may be involved in this viral infection, offering another starting point for research to develop specifically targeted interventions.

These observations suggest there is work for all of us. People with diabetes should be more attentive than others to self-protective actions, particularly handwashing and physical distancing. An adequate supply of insulin and self-care supplies is essential when sheltering in place. Medical providers and health systems can help by assuring reliable access to tools for diabetes self-management. Hospital providers should all know that more severe respiratory illness is associated with diabetes. In-hospital metabolic control may be more difficult when caregivers need personal protective equipment, but newer methods of remotely monitoring glucose patterns could be uniquely helpful. Researchers and clinicians are called upon to follow the clues and find specific interventions. As examples, three additional articles in the current collection in *Diabetes Care* offer expert assessments of important challenges and opportunities posed by COVID-19 (22–24).

The COVID-19 epidemic challenges the entire diabetes community, but the response has been encouraging. As the scale and severity of COVID-19 have become widely known, there has been an outpouring of support for those afflicted. Medical personnel and others on the front lines have shown courage and determination. Virtual interactions, whether on an individual or group basis, are now routine. Health care providers can use this technology to guide the care of their patients, while clinical researchers continue ongoing studies and provide vital medications to study participants. Digital technologies are providing remote access to educational and research meetings and, of course, to loved ones and friends who may be otherwise inaccessible. Until a proven vaccine and highly effective pharmacotherapy are developed, we need widespread testing of apparently well individuals to determine who has immunity from prior infection, who is at risk, and who is unknowingly infected. As the peak of COVID-19 begins to pass and we work to obtain better testing, pharmacotherapy, and ultimately a vaccine, we will enter a longer interval in which we must continue to support the most vulnerable populations—especially older people, those with diabetes or obesity, and those who lack the resources to limit day-to-day exposure to infection. We hope a growing sense of community will help in this task.

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