Diabetes Epidemiology in the COVID-19 Pandemic

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Diabetes has been identified as an important risk factor for mortality and rates of progression to acute respiratory distress syndrome (ARDS) in hospitalized patients with coronavirus disease 2019 (COVID-19). However, many recent reports on this topic reflect hurried approaches and have lacked careful epidemiologic design, conduct, and analysis. Features of prior studies have posed problems for our understanding of the true contribution of diabetes and other underlying comorbidities to prognosis in COVID-19. In this Perspective, we discuss some of the challenges of interpreting the current literature on diabetes and COVID-19 and discuss opportunities for future epidemiologic studies. We contend that the COVID-19 pandemic is a defining moment for the field of epidemiology and that diabetes epidemiology should play a significant role.

As of 1 June, >100,000 people in the U.S. and >3,600,000 people across the world have died of coronavirus disease 2019 (COVID-19), the disease caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This is a defining moment for the field of epidemiology, and the current circumstances are challenging modern epidemiology in fundamental ways.

Epidemiology has been transformed by several major trends. Globalization of the economy and travel has eliminated traditional geographic boundaries, fueled urbanization, and altered nutrition and diet, profoundly changing how infectious and chronic diseases spread. The information age and modern digital communications have fundamentally altered our society and all of the sciences. The advent of the internet, global computer networks, and wireless communication has forever changed our educational and work practices. We have unprecedented speed and capacity for data collection, processing, and analysis.

The COVID-19 pandemic has accelerated many of these trends including reshaping the conduct of studies and their publication. We are experiencing media coverage that is preceding peer-reviewed scientific reports and is occasionally being cited as evidence. There is unparalleled fast-tracking of COVID-19 publications and a dramatic increase in the use of preprint servers (1). The current scientific, professional, and editorial pressures to publish novel reports—and most COVID-19 reports are, by definition, novel—are immense. This rush of publication has resulted in a literature of variable quality and many studies lacking epidemiologic rigor.

IS DIABETES AN INDEPENDENT RISK FACTOR FOR OUTCOMES IN COVID-19? A CASE STUDY IN SOME OF THE CHALLENGES OF COVID-19 EPIDEMIOLOGY

Reports from China and a growing number of studies from Europe and the U.S. have focused on characteristics and outcomes of hospitalized COVID-19 patients. Diabetes has been identified as an important risk factor for mortality and rates of progression to acute respiratory distress syndrome (ARDS) in hospitalized patients with COVID-19.

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Early reports from Wuhan noted a higher prevalence of diabetes among severe cases of COVID-19 (2–4). A high prevalence of diabetes was also noted in reports of COVID-19 hospitalizations in Italian populations (5,6).

Authors have responded to the pressing need for data in a short time frame. However, many studies, including those in published in major medical journals, reflect hurried approaches and have lacked careful epidemiologic design, conduct, and analysis. Features of these studies have posed problems for our understanding of the true contribution of diabetes and other underlying comorbidities to prognosis in COVID-19.

First, what are often being called retrospective cohort studies are actually large case series (7–9). These studies have consisted of convenience samples and selected patients for inclusion on the basis of their outcome status—typically death or survival. Analyses of these data are not truly prospective, as those patients who transferred out of the hospital or who were still in the hospital at the time of the analysis were not included. The reliance on hospitalized cases can also make the disease appear more severe, as more mild cases of COVID-19 are not captured in these samples.

Second, most studies to date have relied on data retrospectively obtained from electronic health records (EHR). This poses several challenges. EHR data are often inaccurate, rife with missing data, and reflective of selective testing. For example, a hospitalized COVID-19 patient with diabetes and a history of cardiovascular disease will be more likely to receive an echocardiogram or troponin testing than other patients. A patient with poorly controlled diabetes will have their glucose measured more often than a patient with good glycemic control who is otherwise similar. The lack of systematic laboratory testing or standardized assessment of risk factors can result in detection bias and other errors, producing spurious associations. Moreover, some studies have cherry-picked associations. For example, one prominent article examined the association of laboratory values on admission in COVID-19 patients with ARDS (2). In this study, the analytic population was restricted to COVID-19 patients with available laboratory measures (complete case analysis) and only those associations that met an arbitrary threshold for significance were reported in the article. Such an approach represents significant reporting bias.

Third, studies of comorbidities have lacked sufficient multivariable adjustment for characteristics of patients at baseline. There has been rampant use of stepwise regression in COVID-19 publications. Stepwise regression is inappropriate in this setting (10,11). To isolate the independent association of any single comorbidity, models need to include demographics and other confounding health conditions. Age and sex are known to be important risk factors for mortality in COVID-19. Yet some early and influential reports from Wuhan did not adjust for either age or sex (2). Also, some studies with age adjustment have modeled age as a simple linear term (4,7,9,12). Modeling age linearly may not fully account for its effect on mortality, as all evidence points to an exponential association (13–16). Obesity and smoking are two important patient characteristics that are also typically poorly characterized in EHR data and have not been included as covariates in many studies.

Fourth, a number of studies have evaluated models that included measurements that change greatly during observation of an acute illness. The development and specification of some of these models have been problematic. For example, studies of risk factors for ARDS and death have adjusted for in-hospital laboratory measurements such as random glucose levels, white cell count, and troponin (17–19). These laboratory measurements are not risk factors in the usual sense, but they may be relevant to outcomes. In-hospital laboratory tests will reflect disease severity and progression, and their associations with outcomes may reflect reverse causality. Alternatively, some metabolic factors that are altered during the course of the disease may causally contribute to outcomes. Studies have identified baseline hyperglycemia, in-hospital glycemic control, and glycemic variability as risk factors for progression and death in patients with diabetes, yet careful measurements of glycemia have not generally been available (4,20). Elevated glucose and glycemic variability are common in acutely ill patients even when they were not known to have diabetes previously. It is not yet clear what these findings mean for the care of patients with COVID-19.

Fifth, some studies have been small with few clinical events, generating highly imprecise statistical estimates. Publication bias is a concern, as small studies with few events are only powered to detect large effects; this can result in false positive results.

Sixth, there have also been concerns about reporting results from the same patients in different articles or even duplicate publications (21). This is problematic for future meta-analyses, as investigators will not be able to determine the independence of study observations. Systematic reviews and meta-analyses will play an important role in synthesizing the literature and pooling data to provide more precise estimates of the effects of diabetes and other comorbidities on outcomes in COVID-19.

Finally, many reports have lacked long-term follow-up. Identifying the frequency of and risk factors for readmission is urgent. We also need surveillance for longer-term outcomes, especially possible pulmonary, neurological, and cardiac sequelae of COVID-19. Understanding morbidity in recovered patients is particularly important in adults with diabetes who are already at higher risk for neurological disorders and diseases of the lung and cardiovascular system.

DIABETES EPIDEMIOLOGY AND COVID-19: WHERE TO GO FROM HERE?

To understand the independent contribution of diabetes on risk of death and ARDS in COVID-19, exposures and covariates need to be measured rigorously and systematically in patients who are not selected with respect to the development of certain outcomes. Regression models need to be thoughtful and reflect our best understanding of the disease. Investigators need to distinguish between clinical characteristics of patients prior to admission (i.e., age, sex, diabetes, cardiovascular disease history, obesity, medication use)—which may be important independent risk factors for prognosis—and in-hospital measures (e.g., inflammation, glucose, troponin), which reflect disease progression. Studies need to be large and community-based, with sufficient follow-up and end points to generate precise estimates. The stakes are substantial. These studies are driving clinical and public health decision-making.

Many of the epidemiologic challenges facing the broader COVID-19 epidemic are applicable to patients with diabetes. Mild cases and deaths have been missed due to undertesting. As a result, it is challenging to estimate infection risk and outcomes for the majority of patients, including those with diabetes. Further, rapid changes in screening policies and approaches make estimating the burden of disease and epidemiologic associations a moving target.

To address these challenges, we need to ask the right questions. From our viewpoint, there are five diabetes-related questions that deserve our attention and should be a focus of future epidemiologic studies.

1) Is Diabetes a Risk Factor for Infection With SARS-CoV-2?

Press coverage of the novel coronavirus has conflated risk factors for infection with SARS-CoV-2 (susceptibility) with risk factors for mortality and disease progression in COVID-19 (prognosis). It is unknown whether diabetes or its complications might directly increase the risk of becoming infected with SARS-CoV-2. It is possible that features of diabetes make individuals physiologically more susceptible to infection with SARS-CoV-2. Indeed, individuals with diabetes are known to be more likely to acquire certain infections (22,23). More likely, however, is that the overlap of diabetes with drivers of health disparities and historical inequities including poverty, racism, housing and residential segregation, environmental risks, and employment and neighborhood factors are causing higher rates of infection (24).

SARS-CoV-2 is disproportionately spreading among our racial and ethnic minority communities and individuals of lower socioeconomic status. The highest rates of hospitalization have been in some of our most vulnerable populations. Concerns have also been raised about bias in COVID-19 treatment. These disparities are long-standing, but the pandemic has brought them to the forefront, including to the pages of the top medical journals and mainstream media reports. In combating this pandemic, it is critical that government and policymakers use this as an opportunity to address some of the fundamental inequities in health care and our social safety net. It is also imperative that, going forward, epidemiologic studies include information on race/ethnicity and rigorous measures of the social determinants of health to best inform policy.

2) Does Diabetes Independently Contribute to Risk of Progression to ARDS and Death in Hospitalized Patients With COVID-19?

Type 2 diabetes is much more prevalent in older age and is a risk factor for chronic kidney disease, cardiovascular disease, and premature mortality. COVID-19 has been described to contribute to cardiac strain and acute myocardial injury. It has not been established whether diabetes itself independently increases risk of progression from mild symptoms to life-threatening illness in COVID-19, or whether associated conditions including obesity, hypertension, and cardiovascular or kidney disease may be driving worse outcomes. These conditions are not likely to be modified after diagnosis of infection, but other aspects of diabetes may be modifiable. Glucose control is important in hospitalized patients and can be modified. Studies that rigorously address the independent associations of diabetes and glycemic control with outcomes of COVID-19 in the intensive care setting are needed.

3) Are There Medications That Are More or Less Effective in Adults With Diabetes in COVID-19?

It is not clear whether disease progression in adults with diabetes and COVID-19 can be modified by diabetes-specific interventions such as intravenous insulin, continuous glucose monitoring, or specific pharmacotherapies. One class of therapies common among adults with diabetes are angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). These medications are recommended for adults with diabetes, hypertension, and proteinuria. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor in host cell membranes to facilitate entry into cells in the lungs and other tissues (25). ACE inhibitors and ARBs increase the abundance of ACE2 receptors, affording more access points for the virus to bind and enter cells (26,27). It has been hypothesized that use of these agents may increase risk of COVID-19 infection and more severe lung injury. In contrast, others have thought these receptors might contribute to viral fixation and lower the risk of infection. This has been a major debate in the field (28). Clinical trials to address these questions are ongoing.

4) What Is the Role of Obesity in COVID-19?

Emerging evidence suggests that obesity is an important risk factor for progression and death in hospitalized adults with COVID-19 (29). The role of overweight and obesity in COVID-19 may relate to ventilation; obesity is a known risk factor for abnormal ventilation and can contribute to reduced functional residual lung capacity and chest wall elastance (30). It is also possible that adiposity may play a direct role, for example, via inflammatory pathways and/or local biological effects of epicardial adipose tissue (31) or other fat depots in the body.

Relying on EHR data will not provide the data we need to address the role of overweight and obesity in this pandemic. At the most basic level, we need studies with systematic measurements of height and weight to rigorously address this question.

5) What Are the Implications of the Pandemic for Diabetes Prevention and Management?

Stay-at-home policies during the pandemic and social distancing have discouraged many activities and changed lifestyles and behavioral patterns in large swaths of the population. There have been anecdotal reports of increased consumption of unhealthy foods and weight gain. Elective procedures, preventive outpatient visits, and ambulatory maintenance care are being delayed. Routine care including diabetes screening and recommended routine screening for complications and HbA_{1c} testing in patients with diabetes have been deferred for millions of patients. There have also been reductions in hospitalizations for myocardial infarction and other acute events, likely as a result of patients avoiding the health care system and forgoing care due to fear of SARS-CoV-2 transmission (32–34). Implications of this deferred care on short- and long-term complications of diabetes will be an important topic of subsequent research.

Recent reports have provided helpful guidance on management of mild COVID-19

disease (the majority of cases) in the setting of diabetes (35). An unfortunate challenge is that the pandemic has caused problems of access to medications for some patients. Whereas, a promising trend is that telemedicine has been widely adopted and represents a particular opportunity for diabetes medicine, as aspects of diabetes care may lend themselves well to telemedicine technology. The pandemic has also fueled interest in remote monitoring technologies; continuous glucose monitoring devices are poised for adoption for such purpose (36).

Social isolation and loneliness as a result of stay-at-home policies and social distancing are concerns. The psychological consequences of the pandemic are likely to disproportionately affect older adults and those with preexisting health conditions including diabetes. Older age and diabetes are known risk factors for depression (37). The psychosocial effects of the physical isolation that has accompanied the pandemic and measures of mental health and well-being during this global pandemic are important considerations for future studies.

CONCLUSIONS

The COVID-19 epidemic represents an unprecedented challenge to patients with chronic disease, especially diabetes. Epidemiology has never been more important. Epidemiologists are public health professionals who typically toil in the background. We have now been foisted to the forefront of the pandemic, to television news and the front covers of newspapers. When public health interventions work, they are seamless and invisible, preventing the spread of disease and improving health without any front-page headlines. The pandemic has made our "invisible profession" of public health highly visible. We are at the beginning of this pandemic. For many aspects, we don't even know what we don't know. But we do know that this is the moment for team science—for interdisciplinary groups to come together to identify the most important questions and address them with rigor and responsible research.

Prospective studies with systematic data collection and extended follow-up, surveys with probability sampling of the general population, randomized clinical trials of therapeutic approaches, and collaborative studies in diverse populations are needed. Sound epidemiologic thinking is indispensable to the design of those studies that will answer questions central to the COVID-19 pandemic and inform clinical and public health policy. This pandemic has already shown us that individuals with diabetes are a vulnerable population who need particular consideration. Diabetes epidemiology should play a significant role in helping address this public health crisis.

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