COVID-19, Hyperglycemia, and New-Onset Diabetes

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Certain chronic comorbidities, including diabetes, are highly prevalent in people with coronavirus disease 2019 (COVID-19) and are associated with an increased risk of severe COVID-19 and mortality. Mild glucose elevations are also common in COVID-19 patients and associated with worse outcomes even in people without diabetes. Several studies have recently reported new-onset diabetes associated with COVID-19. The phenomenon of new-onset diabetes following admission to the hospital has been observed previously with other viral infections and acute illnesses. The precise mechanisms for new-onset diabetes in people with COVID-19 are not known, but it is likely that a number of complex interrelated processes are involved, including previously undiagnosed diabetes, stress hyperglycemia, steroid-induced hyperglycemia, and direct or indirect effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the β-cell. There is an urgent need for research to help guide management pathways for these patients. In view of increased mortality in people with new-onset diabetes, hospital protocols should include efforts to recognize and manage acute hyperglycemia, including diabetic ketoacidosis, in people admitted to the hospital. Whether new-onset diabetes is likely to remain permanent is not known, as the long-term follow-up of these patients is limited. Prospective studies of metabolism in the setting of postacute COVID-19 will be required to understand the etiology, prognosis, and treatment opportunities.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that results in the clinical disease coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan, China, and has claimed over 2 million lives globally (1). Certain chronic comorbidities, such as hypertension, cardiovascular disease, obesity, diabetes, and kidney disease, are highly prevalent in people with COVID-19. While these comorbidities do not appear to increase the risk of developing COVID-19, they are associated with an increased risk of a more severe case of the condition as well as mortality (2).

HYPERGLYCEMIA AND NEW-ONSET DIABETES ASSOCIATED WITH COVID-19

Severe hyperglycemia is common in critically ill patients and is often seen as a marker of disease severity (3). Several studies over the course of the pandemic have reported that COVID-19 is associated with hyperglycemia in people with and without known diabetes (4,5). One study from Wuhan of hospitalized, mainly elderly COVID-19 patients reported that 21.6% had a history of diabetes, and, based on the first glucose measurement upon admission, 20.8% were newly diagnosed with diabetes (fasting admission glucose ≥7.0 mmol/L and/or

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HbA_{1c} ≥6.5%), and 28.4% were diagnosed with dysglycemia (fasting glucose 5.6–6.9 mmol/L and/or HbA_{1c} 5.7–6.4%) (5).

A number of studies have reported new-onset diabetes (that phenotypically could be classified as either type 1 diabetes [T1D] or type 2 diabetes [T2D]) as being associated with the presence of COVID-19 (Table 1). A study from London, U.K., reported 30 children aged 23 months to 16.8 years with new-onset T1D (6). Of these, 70% presented with diabetic ketoacidosis (DKA), 52% with severe DKA, and 15% with a positive COVID-19 test (6). The authors concluded that this represented an 80% increase in new-onset T1D during the pandemic compared with previous years (6). Further, it would also appear that the severity of presentation of youth with T1D is increased (7). Conflicting results have also been reported, however, with data from 216 pediatric diabetes centers in Germany showing no increase in the number of children diagnosed with T1D during the early months of the pandemic (8). However, the same centers reported data on 532 children and adolescents with newly diagnosed T1D and found significant increases in DKA and severe ketoacidosis at diagnosis during the same time period (9).

A few studies have also observed that DKA and hyperosmolar hyperglycemic state are unusually common in COVID-19 patients with known diabetes (10–13). In a Chinese study, 42 patients had COVID-19 and ketoacidosis, and 27 had no prior diagnosis of diabetes (12). A study from London, U.K., included 35 patients with COVID-19 who presented with DKA (31.4%), mixed DKA and hyperosmolar hyperglycemic state (HSS; 31.7%), HSS (5.7%), or hyperglycemic ketoacidosis (25.7%) (14). Overall, 80% had T2D. Of those with T2D, the prevalence of DKA was high, indicating insulinopenia in people with COVID-19. In addition, 5.7% of the 35 patients with COVID-19 had newly diagnosed diabetes. DKA was protracted in people with COVID-19 compared with previous reports of those with non–COVID-19 DKA (35 h vs. 12 h), and they had a higher insulin requirement (14). Another recent U.S. study of 5,029 patients (mean age 47 years) from 175 hospitals found that patients with COVID-19 had higher BMI, higher insulin requirement, prolonged time to resolution of DKA, and higher mortality than those without COVID-19 (15). A U.K. study reported that children presented more frequently with DKA than during the prepandemic period (10% severe prepandemic vs. 47% during the first wave of the pandemic) and had higher HbA_{1c} (13% vs. 10.4%) (7).

A number of studies have also reported that preexisting diabetes as well as newly diagnosed diabetes with a first glucose measurement on hospital admission are both associated with an increased risk of all-cause mortality in hospitalized patients with COVID-19. In a systematic review of 3,711 COVID-19 patients from 8 studies (492 patients with new-onset diabetes), the pooled prevalence of new-onset diabetes was 14.4% (95% CI 5.9–25.8%) from a random-effect meta-analysis (16). Worryingly, the risk of mortality appears to be higher in people with new-onset diabetes than with COVID-19 patients with known diabetes (5,17). An Italian study of 271 people admitted with COVID-19, 20.7% of whom had preexisting diabetes, found that hyperglycemia was independently associated with mortality (hazards ratio [HR] 1.80, 95% CI 1.03–3.15). The study also showed that people with diabetes and hyperglycemia had worse inflammatory profiles (18). In a study from Wuhan, China, patients with newly diagnosed diabetes were more likely to be admitted to the intensive care unit, require invasive mechanical ventilation, have a high prevalence of acute respiratory distress syndrome, acute kidney injury, or shock, and have the longest hospital stays (5). The study also reported data showing that glucose levels at hospital admission in people with newly diagnosed diabetes and in those with a history of diabetes were both associated with the increased risk of all-cause mortality (5). Patients with newly diagnosed diabetes had a higher mortality than COVID-19 patients with known diabetes, hyperglycemia (fasting glucose 5.6–6.9 mmol/L and/or HbA_{1c} 5.7–6.4%) or normal glucose (HR 9.42, 95% CI 2.18–40.7). This is one of a few studies where HbA_{1c} was measured on admission to determine whether newly diagnosed diabetes was present in asymptomatic patients prior to admission or whether those who developed it did so following admission (5).

TYPE OF DIABETES

It is currently unclear whether the new-onset diabetes associated with COVID-19 is type 1, type 2, or a complex subtype of diabetes. Although in T1D insulin deficiency is usually the result of an autoimmune process, in SARS-CoV-2 infection it could be due to destruction of the β-cells. Unfortunately, studies of islet cell antibodies in people with new-onset diabetes have been limited to a few case reports (19,20). Multiple studies have reported a high number of incidents of DKA in people with and without COVID-19, suggesting a direct effect of SARS-CoV-2 on pancreatic β-cells. One study of hospitalized patients with SARS-CoV-1 infection showed that immunostaining for angiotensin-converting enzyme 2 (ACE2) protein was strong in pancreatic islets but weak in exocrine tissues (21). However, a recent study from India compared new-onset diabetes in hospitalized patients prior to COVID-19 with new-onset diabetes during COVID-19 and found worse glycemic parameters in new-onset diabetes during COVID-19 and diabetes but no difference in symptoms, phenotype, or C-peptide levels (22).

POTENTIAL MECHANISMS FOR NEW-ONSET DIABETES

The precise mechanisms behind the development of new-onset diagnosis in people with COVID-19 are not known, but it is likely that a number of complex, interrelated etiologies are responsible, including impairments in both glucose disposal and insulin secretion, stress hyperglycemia, preadmission diabetes, and steroid-induced diabetes (Fig. 1). One recent article reported an increase in the number of children admitted to pediatric intensive care unit with new-onset T1D with severe DKA and a smaller increase in incidence of new-onset T1D (23). Overall, 7/20 (35%) of the children diagnosed in 2020 were tested for SAR-CoV-2, with all being negative. The authors suggested that the increase in incidence and severity were due to altered presentation during the pandemic rather than direct effects of COVID-19. Current data also suggest a bidirectional relationship between T2D and COVID-19 (24), but whether there is a bidirectional relationship between hyperglycemia and COVID-19

Table 1—Studies reporting new-onset diabetes

Reference	Country	Design	Population	Results
Li et al. (5)	China	Retrospective observational	453 patients with laboratory-confirmed SARS-CoV-2 infection aged 61 (IQR 49, 68) years	94 patients (21%) were newly diagnosed with diabetes (fasting admission glucose ≥7.0 mmol/L and/or HbA_{1c} ≥6.5%)
Unsworth et al. (6)	U.K.	Cross-sectional	33 children aged 10.9 (IQR 6.8) years, 68% male, 36% White European	30 children (91%) presented with new-onset T1D; 5 children tested positive for SARS-CoV-2; 70% presented with DKA and 52% with severe DKA
Ebekozien et al. (17)	U.S.	Cross-sectional	64 children and adults aged 20.9 (SD 14.84) years, 61% female, 48.4% non-Hispanic White	6 patients (9.8%) had new-onset T1D, with 5 (15.6%) in the COVID-19–positive group
Tittel et al. (8)	Germany	Prospective study	Pediatric T1D patients with onset age between 6 months and <18 years diagnosed between 13 March and 13 May in each year between 2011 and 2020 (from German Diabetes Registry data)	T1D incidence (per 100,000 patient-years) increased from 16.4 in 2011 to 22.2 in 2019; the incidence in 2020 (23.4) did not significantly differ from the predicted value
Armeni et al. (14)	U.K.	Retrospective case series	35 patients with SARS-CoV-2 infection aged 60 (IQR 45, 70) years, 22.9% female, 20% Caucasian; inclusion criteria were *1*) hospitalization with confirmed COVID-19 diagnosis, *2*) DKA and/or hyperosmolar hyperglycemic state at presentation, *3*) known or new diagnosis of diabetes and presence of ketonemia, and *4*) Glasgow coma scale of at least 12 on admission	28 (80%) patients had T2D, and 2 (5.7%) were new presentations of diabetes
Sathish et al. (16)	China, Italy, U.S.	Systematic review and meta-analysis	From 8 studies, 3,711 COVID-19 patients, aged between 47 and 64.9 years, 53.3–80.0% male	492 patients had newly diagnosed diabetes, and random-effect meta-analysis estimated a pooled prevalence of new-onset diabetes of 14.4% (95% CI 5.9–25.8%)
Wang et al. (64)	China	Retrospective study	605 patients with SARS-CoV-2 infection, aged 59.0 (IQR 47.0, 68.0) years, 46.8% female; exclusion criteria were *1*) no definitive 28-day outcome since transfer to another hospital, *2*) missing key clinical information, *3*) no FBG data available at admission, and *4*) having previously diagnosed diabetes	176 patients (29.1%) with new-onset/newly detected diabetes

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Table 1—Continued

Reference	Country	Design	Population	Results
Yang et al. (65)	China	Retrospective cohort study	69 patients with laboratory-confirmed SARS-CoV-2 infection aged 61 (IQR 52, 57) years, 49.3% male; exclusion criteria were patients receiving glucocorticoid treatment or with a history of diabetes, myocardial infarction, heart failure, dialysis, renal transplant, or cirrhosis and patients missing basic medical information	In critical and moderate + severe patients the prevalence of new-onset diabetes was 53.85% and 13.95%, respectively
Fadini et al. (66)	Italy	Retrospective study	413 patients with SARS-CoV-2 infection aged 64.9 (SD 15.4) years, 59.3% male	21 patients (5%) with new-onset/newly detected diabetes
Wu et al. (46)	Australia	Retrospectively analyzed	8 patients with T2D were admitted to the intensive care unit with COVID-19; 5 had preexisting diabetes	Within patients with newly diagnosed diabetes, C-peptide levels and negative anti-GAD antibodies were found, consistent with T2D, and HbA_{1c} ranged from 11.1% to 12.4% (98 to 112 mmol/mol)
Ghosh et al. (22)	India	Retrospective cohort	555 patients with new-onset diabetes were included, with 282 with new-onset diabetes prior to the COVID-19 pandemic (19 September to 20 February) and 273 with new-onset diabetes during COVID-19 (April–October 20)	Patients with new-onset diabetes during the COVID-19 pandemic had higher fasting and postprandial blood glucose, glycated hemoglobin levels, and C-peptide vs. patients with new-onset diabetes prior to pandemic; no differences were seen in C-peptide or glycemic outcomes in the patients with new-onset diabetes between those who tested positive or negative for COVID-19 (antibody test)
Zhang et al. (67)	China	Retrospective study	312 patients with COVID-19 with a mean age of 57 (IQR 38, 66) years; 55% were female, 84 had diabetes, and 36 were new diagnoses (57 had fasting glucose levels $\geq$7.0 mmol/L, including 30 without and 27 with a known history of diabetes); exclusion criteria included no positive COVID-19 test, patients remaining in hospital, and missing information on clinical outcomes because of transfer to other hospitals	Diabetes at admission was associated with higher risks of adverse outcomes among patients with COVID-19 (irrespective of whether or not the diagnosis was new)

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Table 1—Continued

Reference	Country	Design	Population	Results
Smith et al. (68)	U.S.	Retrospective study	184 patients hospitalized for COVID-19, aged 64.4 years (range 21–100), 67.7% female	6 patients without diabetes and with normal HbA_{1c} levels also had repeatedly elevated fasting blood glucose; these 29 patients had fasting blood glucose levels consistent with new-onset diabetes and temporally associated with recent acquisition of SARS-CoV-2 infection
Liu et al. (69)	China	Retrospective study	In total, 233 patients were included in the final analysis; 80 (34.3%) patients had diabetes, among whom 44 (55.0%) were previously diagnosed and 36 (45.0%) were newly defined as having undiagnosed diabetes with an HbA_{1c} level ≥6.5% (48 mmol/mol) at admission	Risk of in-hospital death was significantly increased in all patients with diabetes (HR 3.80, 95% CI 1.71–8.47), those with diagnosed diabetes (HR 4.03, 95% CI 1.64–9.91), and those with undiagnosed diabetes who were newly defined by HbA_{1c} testing at admission (HR 1.89, 95% CI 1.18–3.05) compared with those without diabetes

IQR, interquartile range.

is not known (Fig. 2). The following sections give more detailed discussions of some of the proposed mechanisms for new-onset diabetes associated with COVID-19.

Preexisting Undiagnosed Diabetes

One reason for new-onset diabetes is that these patients may have had undetected diabetes prior to admission, potentially as a consequence of recent weight gain due to changes in lifestyle and worsening of hyperglycemia mainly due to self-isolation, social distancing, reduced physical activity, and poor diets as a result of mental health issues. For example, a recent survey of 155 countries showed that 53% of individuals had reduced their preventative- and service-level access for noncommunicable diseases either partly or completely (25). These lifestyle changes could lead to insulin resistance, which would further trigger inflammatory pathways, leading to new-onset diabetes.

Stress Hyperglycemia and New-Onset Diabetes Following Acute Illness

The phenomenon of hyperglycemia and new-onset diabetes following admission to the hospital with acute illness is not new and was previously observed during the SARS-CoV-1 outbreak, where new-onset diabetes without glucocorticoid use on admission was also associated with increased mortality (26). Stress hyperglycemia is a sign of relative insulin deficiency, which is associated with increased lipolysis and increased circulating free fatty acids seen in acute illness such as myocardial infarction or severe infections (27). In COVID-19, stress hyperglycemia may be even more severe due to the cytokine storm.

Studies have shown that patients with newly diagnosed diabetes have higher levels of inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, and white blood cells (5). Acute inflammation seen in cytokine storm may worsen insulin resistance (10), with one study showing neutrophils, D-dimers, and inflammatory markers being significantly higher in those with hyperglycemia than in those with normal glucose (18). People with obesity are also at risk for diabetes and severe outcomes related to COVID-19 (28), with adiposity being a driver for impaired glucose metabolism, immune responses, and inflammation (10).

Previous studies have reported stress hyperglycemia after several acute conditions, including myocardial infarction. However, there have been difficulties in interpretation of these studies due to the variable definitions used to define new-onset diabetes and stress hyperglycemia. One systematic review of 15 studies of patients admitted with myocardial infarction without diabetes with a glucose level in the range 6.1–8.2 mmol/L was associated with a 3.5-fold (95% CI 2.9–5.4) higher risk of death than that for patients without diabetes with lower glucose concentrations (27). This meta-analysis also reported that glucose values in the range of 8.0–10.0 mmol/L on admission were associated with an increased risk of congestive heart failure or cardiogenic shock in people without diabetes (27), and the risk of death was increased by 70% (relative risk 1.7, 95% CI 1.2–2.4) (27). Stress hyperglycemia following myocardial infarction has also been shown to be associated with an increased risk of in-hospital mortality in patients with and without diabetes (27). Another systematic review of 43 studies totaling 536,476 patients showed that stress

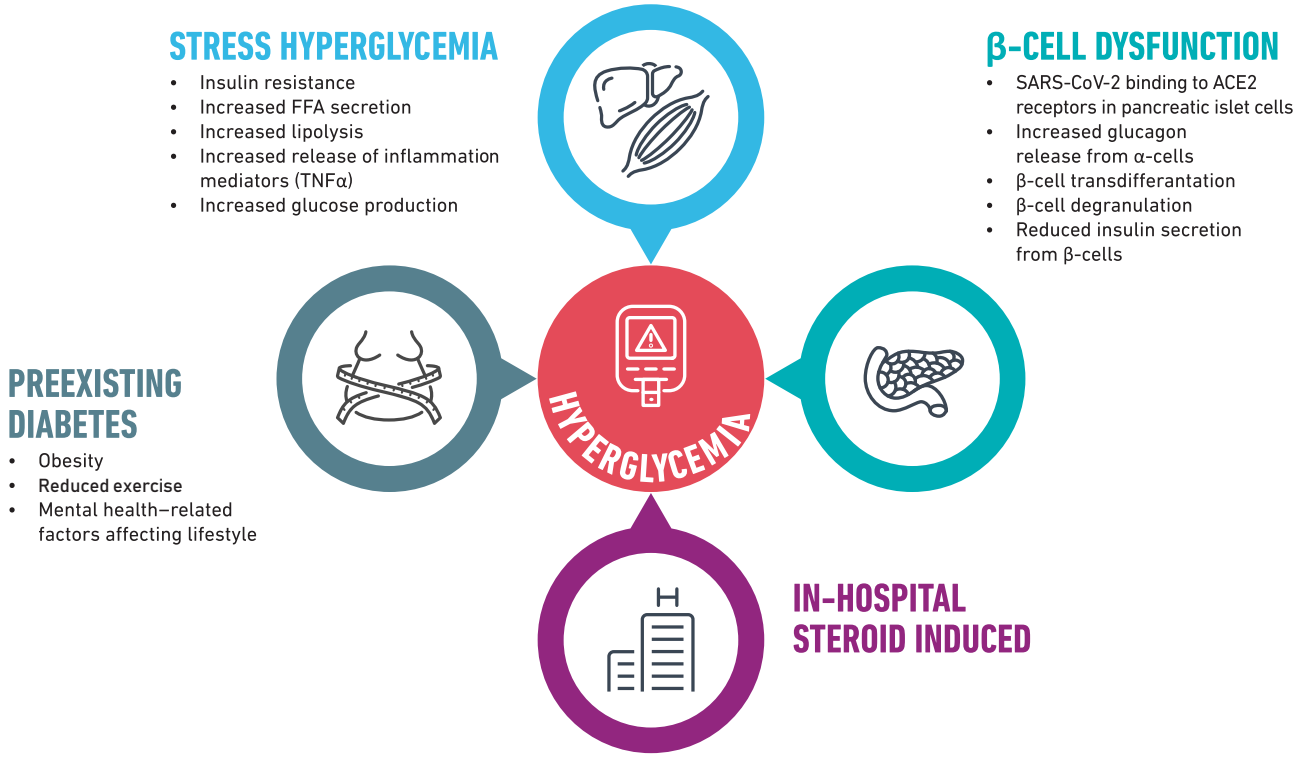

Figure 1—Potential mechanisms for development of new-onset diabetes in people with COVID-19.

hyperglycemia was associated with increased mortality, intensive care unit admission, hospital length of stay, and mechanical ventilation (29).

Although stress-related hyperglycemia in acutely ill hospitalized patients occurs in many settings, the data related to new-onset diabetes due to SARS-CoV-2 seem to suggest that the prevalence is disproportionate compared with data from populations admitted with other acute illnesses (16). A number of studies have reported stress hyperglycemia following critical acute illness; however, only a few studies have followed these patients beyond hospitalization to determine if the stress hyperglycemia is transient or indicative of new-onset diabetes. One meta-analysis of four cohort studies with 2,923 participants included 698 (23.9%) people with stress hyperglycemia. On follow-up more than 3 months after hospital discharge, 131 cases or 18.8% of people with stress hyperglycemia were identified with

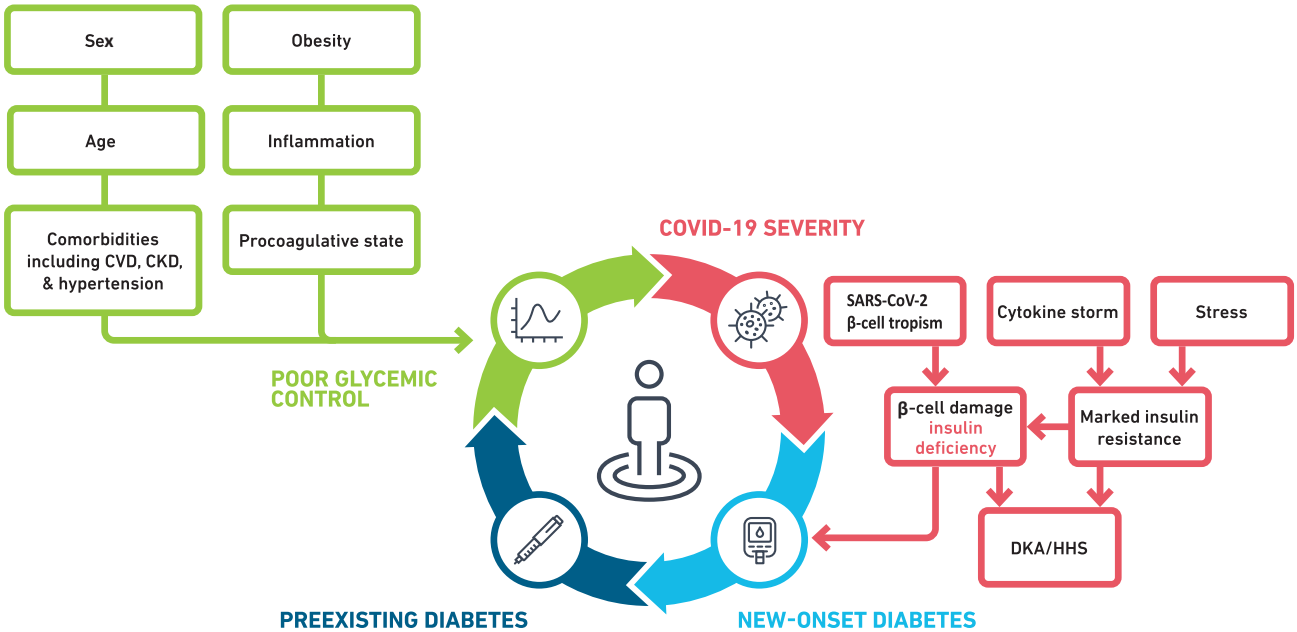

Figure 2—Bidirectional relationship between T2D, hyperglycemia, and COVID-19. CVD, cardiovascular disease; CKD, chronic kidney disease; HHS, hyperosmolar hyperglycemic syndrome.

newly diagnosed diabetes, and stress hyperglycemia was associated with an increased incidence of diabetes (odds ratio [OR] 3.48, 95% CI 2.02–5.98) (30). However, three studies defined stress hyperglycemia as blood glucose of ≥7.8 mmol/L, and one database study defined it as a glucose of >11.1 mmol/L. Furthermore, the timing of glucose measurement was not reported in any of these studies.

Viral Infections and New-Onset Diabetes

Viral infections may have a direct or indirect effect on the pancreas. Previous studies have reported acute inflammation in the pancreas due to other viruses, such as human immunodeficiency virus, mumps, measles, cytomegalovirus virus, herpes simplex virus, and hepatitis virus (13). A meta-analysis of 24 case-control studies showed that enterovirus infection was significantly associated with T1D-related autoimmunity (OR 3.7, 95% CI 2.1–6.8) and clinical T1D (OR 9.8, 95% CI 5.5–17.4) (31). Another meta-analysis of 34 studies showed that there was a significantly increased risk of T2D with hepatitis C viral infection compared with noninfected control subjects in both retrospective (OR 1.68, 95% CI 1.15–2.20) and prospective (OR 1.67, 95% CI 1.28–2.06) studies. The excess risk was also observed compared with hepatitis B virus–infected control subjects (OR 1.80, 95% CI 1.20–1.40) (32). Studies of human islet cells have shown that coxsackie B viruses cause functional impairment or β-cell death (33).

Acute hyperglycemia with coronavirus infection has been linked to the binding of the coronavirus to the ACE2 receptor in the pancreatic islet cells (30). ACE2 expression has been shown to be higher in the pancreas than the lungs and expressed in both exocrine glands and the islets of the pancreas, including β-cells (34,35). However, the evidence for ACE2 expression in pancreatic cells is conflicting, with studies suggesting ACE2 expression in a limited subset of β-cells (36). Data from human pancreatic tissues identified ACE2 expression in pancreatic ductal epithelium and microvasculature and concluded that SARS-CoV-2 infection of pancreatic endocrine cells (including β-cells) is unlikely to be a central mechanism related to diabetes (37). Alternatively, the proinflammatory cytokines and acute-phase reactants due to COVID-19 could directly cause inflammation and damage to pancreatic β-cells (38).

A cytokine storm in people infected with SARS-CoV-2 is a prothrombotic, highly inflammatory pathological state that can have direct and indirect effects on pancreatic β-cells. An autopsy study of three patients who died of COVID-19 in China reported they had degeneration of islets (39). A study from Wuhan of 121 COVID-19 patients showed that even patients with mild COVID-19 had increased levels of amylase and lipase (1.85%), although people with severe COVID-19 had much higher levels (17%) (34). Some patients also had symptoms of acute pancreatitis. In this study, computed tomography scans of people with severe COVID-19 showed changes in the pancreas that comprised mainly enlargement of the pancreas or dilation of the pancreatic duct without acute necrosis (34). A recent study of gene and protein expression in live human pancreatic cultures and postmortem pancreatic tissue from COVID-19 patients observed that SARS-CoV-2 can infect pancreatic cells and indicated that endocrine islets and exocrine acinar and ductal cells within the pancreas allow SARS-CoV-2 entry (40). Another study reported that the SARS-CoV-2 receptor and ACE2 and related entry factors are expressed in the pancreatic β-cells, and in COVID-19 patients they infect β-cells, attenuate pancreatic insulin levels and secretion, and induce β-cell apoptosis (41).

In-Hospital Steroid-Induced Hyperglycemia

Steroid-induced hyperglycemia is common in hospitalized patients. Previous studies show that 53–70% of individuals without diabetes develop steroid-induced hyperglycemia (42). An Australian study of 80 hospitalized people without diabetes reported that 70% of subjects had at least one blood glucose measurement of ≥10 mmol/L (43). A meta-analysis of 13 studies showed that overall, 32.3% of people developed glucocorticoid-induced hyperglycemia and 18.6% developed diabetes (44). Use of steroids, particularly following the publication of the RECOVERY trial with the use of dexamethasone in people admitted to the hospital with COVID-19, may therefore also be associated with an increased risk of developing diabetes, which again could be directly related to steroid-induced abnormalities with delayed or blunted recovery of βcell damage (10).

MANAGEMENT OF PEOPLE WITH NEW-ONSET DIABETES FOLLOWING COVID-19

As the precise mechanisms and epidemiology of new-onset diabetes related to COVID-19 are not known, it is difficult to guide management pathways for these patients. However, in view of increased mortality in people with new-onset diabetes and in those with elevated glucose at admission, hospital protocols should include management of acute hyperglycemia. It is also imperative to recognize new-onset diabetes and manage DKA in people admitted to the hospital to improve outcomes. These patients frequently also require higher doses of insulin than those with acute illness caused by other conditions or non–COVID-19 DKA (18,45,46).

Whether hospital admission of new-onset diabetes is likely to remain permanent is not known, as long-term follow-up of these patients is limited. People with stress hyperglycemia may revert to normoglycemia following the recovery from acute illness and, therefore, may not be classed as having diabetes or requiring any glucose-lowering medication; they will require follow-up to determine if the new-onset diabetes is indeed permanent.

Although there are no data on follow-up of newly diagnosed people with diabetes related to COVID-19, one systematic review of four cohort studies with a 3-month follow-up reported 18.8% with newly diagnosed diabetes in those who were diagnosed with in-hospital hyperglycemia. However, studies differed in their definitions of stress hyperglycemia, participants included, and follow-up (30). In another prospective study, 181 consecutive patients admitted with myocardial infection in Sweden with an admission glucose of ≥11.1 mmol/L had a 75-g oral glucose tolerance test at 3 months postdischarge (47). Overall, 35% and 40% of patients, respectively, had impaired glucose tolerance at discharge and at 3 months postdischarge, and 31% and 25%, respectively, had new-onset diabetes (47).

A recent case series from India reported that three individuals who had

COVID-19 and developed acute-onset diabetes and DKA initially responded to treatment with intravenous fluid and insulin. They were then transitioned to multiple doses of subcutaneous insulin, and, at follow-up of 4–6 weeks, all had their insulin stopped and were initiated on oral glucose-lowering agents (20). Two patients had GAD antibody measured and were both negative. Although new-acute-onset diabetes with DKA in adults would normally indicate T1D, these case data suggest that these patients have had a transient insulinopenia.

Persistent diabetes in COVID-19 patients may also be related to "long COVID," also known as post–COVID-19 syndrome or post-acute sequelae of COVID-19 (PASC), defined as persistence of symptoms beyond 3 months postinfection. It frequently affects multiple organ systems and is estimated to affect 10% of COVID-19 patients (48,49). Long COVID is complex due to varying symptoms and pathophysiology (48,49) but may be due to immune and inflammatory responses seen in many severe acute viral infections (49). The risks of cardiorenal complications are high in people admitted with COVID-19, and a meta-analysis of 44 studies showed that the prevalence of cardiorenal complications is high in people with long COVID, with acute cardiac injury occurring in 15%, venous thromboembolism in 15%, and acute kidney injury in 6% (50).

As risk factors for poor outcomes in people with COVID-19 include obesity, hyperglycemia, and cardiovascular and renal disease, glucose-lowering agents that improve metabolic function without weight gain would be preferable for long-term management of people following acute COVID-19 infection and sustained symptoms (i.e., long COVID). Novel therapeutic options include sodium–glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1RAs), particularly as cardiovascular outcome trials in people with T2D have confirmed benefits on weight, glycemic control, and cardiovascular events, including cardiovascular death and renal outcomes (51). SGLT2i have also been shown to reduce hospitalization for heart failure and may reduce the risk of death from noncardiovascular causes (51). However, data for these therapies in management of patients with long COVID are lacking.

The DARE-19 study investigating the safety of dapagliflozin in people admitted to the hospital with COVID-19 have recently been reported (52). The study showed that the primary end points were not achieved; namely, dapagliflozin did not prevent organ dysfunction (pulmonary, cardiac, or renal) or death and did not improve clinical recovery within 30 days following commencing the medication. However, DKA was reported in two patients with T2D of the 625 patients in the dapagliflozin arm, with the events being nonsevere and resolving after study medication discontinuation. Other therapeutic trials are ongoing with dipeptidyl peptidase 4 inhibitors, pioglitazone, and the GLP-1RA semaglutide (53–58).

Long-term follow-up of patients with COVID-19 and hyperglycemia will therefore be required to determine whether they would still need glucose-lowering agents. A recent study from China reported new-onset diabetes in 3.3% of 1,733 people at 6 months following discharge from hospital with COVID-19 (59). Another study from England of 47,780 people discharged from hospital following admission for COVID-19 showed 4.9% developed diabetes at a mean follow-up of 140 days (60). Another study using a national health care database of the U.S. Department of Veterans Affairs reported a higher burden of new-onset diabetes 6 months following COVID-19 (61). However, none of these studies reported any further details regarding new-onset diabetes, including type of diabetes. COVID-19–related hyperglycemia and new-onset diabetes are new findings and of great interest globally. However, it remains to be seen if hyperglycemia associated with COVID-19 is indeed associated with a higher prevalence of new-onset diabetes after acute and chronic illness. The diagnosis of diabetes will need to be based on fasting glucose, 2-h post–oral glucose tolerance test, or HbA_{1c} as recommended by international guidelines (62). Previous studies have demonstrated that new-onset diabetes is associated with the level of in-hospital hyperglycemia. One systematic review of 18 studies (111,078 patients) admitted with acute or chronic illness reported new-onset diabetes in 4% (95% CI 2–7%), 12% (95% CI 9–15%), and 28% (95% CI 18–39%) of patients with in-hospital normoglycemia, mild hyperglycemia, and severe hyperglycemia, respectively (3). Studies in the meta-analysis had a mean follow-up of 3–60 months without significant effect on diabetes incidence.

It will also be important to continue long-term surveillance of people with new-onset diabetes to ensure their risk factors are managed and that they achieve good glycemic control, as many may also have other symptoms of long COVID. Stress hyperglycemia due to acute critical illness may also identify patients who are already at high risk of diabetes, and therefore early diagnosis, interventions, and long-term follow-up of complications are essential for these patients. Whether screening everyone following a diagnosis of COVID-19 for diabetes and prediabetes would identify a significant number of people or is cost-effective remains to be seen. However, there may be a case for this, as many international guidelines recommend screening high-risk populations for diabetes and prediabetes and, if identified, to then manage people with diabetes according to international guidelines or lifestyle intervention of people with prediabetes. In view of the associated cardiovascular and renal damage following COVID-19, these patients should have regular monitoring of cardiovascular and kidney risk factors with a view to tight risk factor control. These patients may also benefit from regular screening for microvascular and macrovascular complications.

FUTURE RESEARCH RECOMMENDATIONS

New-onset diabetes in relation to COVID-19 is a new phenomenon and provides an opportunity to observe these patients longer term and conduct research studies that include epidemiological and interventional approaches. An international group of researchers have already established a global registry of patients with new-onset COVID-19–related diabetes, called the CoviDIAB Project, and will report on findings in future (63). However, further international collaborative research programs are urgently needed to understand the natural disease epidemiology of COVID-19.

Recommendations for future studies should include the following:

- Multicenter prospective cohort studies following these patients for several

years to assess the trajectory of new-onset diabetes with COVID-19 and quantify whether the risks of admission-related hyperglycemia and new-onset diabetes with COVID-19 are different from usual-onset diabetes.
- Investigation of pathophysiology by cross-sectional and prospective studies to assess β-cell function and insulin resistance in people with COVID-19 related to new-onset diabetes.
- Experimental studies of direct effects of SARS-CoV-2 on pancreatic β-cells and other islet cell types.
- Assessment of inflammatory markers to get full understanding of new-onset COVID-19–related diabetes.
- Development and validation of methods of screening for diabetes in people who have developed COVID-19–related hyperglycemia.
- Modeling of cost-effectiveness of targeted screening of people following COVID-19.
- Evaluation of management plans and models of care that may be appropriate to this phenomenon.
- Determination of prevalence and impact of long COVID in people with new-onset diabetes.
- Comparisons of longer-term outcomes of people with COVID-19–related new-onset diabetes with new-onset diabetes due to other acute illnesses (such as other infections and myocardial infarction).
- Understanding of the benefits and cost-effectiveness of use of different therapeutic options, including novel therapies such as SGLT2i and GLP-1RAs.

CONCLUSIONS

Recently published studies suggest that COVID-19 is associated with new-onset diabetes; therefore, there is potential to identify and manage these people early, with the aim of improving long-term outcomes. Whether elevated glucose concentrations (in a non-diabetes range) or new-onset diabetes is due to immune-mediated and inflammatory responses, the direct effect of SARS-CoV-2 on β-cells, or a complex combination of mechanisms, is not known. The majority of studies have mainly assessed patients who have been hospitalized with COVID-19, and there are no or limited data on patients with milder illness managed in the community. There are also no data on long-term outcomes of people with diabetes and COVID-19 and their risk of long COVID. New-onset diabetes with SARS-CoV-2 infection also appears to be a complex syndrome associated with a number of pathophysiological mechanisms and, given we are still in the midst of a global COVID-19 pandemic, are likely to see even larger numbers of people globally with new-onset diabetes. International efforts need to be established to study COVID-19–associated new-onset diabetes with follow-up of large numbers of patients.

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