COVID-19 and Diabetes: A Collision and Collusion of Two Diseases

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The coronavirus disease 2019 (COVID-19) pandemic has infected >22.7 million and led to the deaths of 795,000 people worldwide. Patients with diabetes are highly susceptible to COVID-19–induced adverse outcomes and complications. The COVID-19 pandemic is superimposing on the preexisting diabetes pandemic to create large and significantly vulnerable populations of patients with COVID-19 and diabetes. This article provides an overview of the clinical evidence on the poorer clinical outcomes of COVID-19 infection in patients with diabetes versus patients without diabetes, including in specific patient populations, such as children, pregnant women, and racial and ethnic minorities. It also draws parallels between COVID-19 and diabetes pathology and suggests that preexisting complications or pathologies in patients with diabetes might aggravate infection course. Finally, this article outlines the prospects for long-term sequelae after COVID-19 for vulnerable populations of patients with diabetes.

The coronavirus disease 2019 (COVID-19) pandemic has infected >22.7 million and killed >795,000 people worldwide, as of 21 August 2020 (1). COVID-19 infection is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA β-coronavirus (2). Patients with diabetes are highly susceptible to adverse outcomes and complications of COVID-19 infection (3). The COVID-19 pandemic is superimposing on the preexisting diabetes pandemic to create large and significantly vulnerable populations of patients with COVID-19 and diabetes. Other comorbid conditions frequent in patients with type 2 diabetes, e.g., cardiovascular disease (CVD) and obesity, also predispose COVID-19 patients to adverse clinical outcomes (4,5).

SARS-CoV-2 pathophysiology remains incompletely understood, but evidence suggests it triggers hyperinflammation in certain patients (6) and that tissue tropism is exhibited (7), pathologies shared with chronic inflammation and multitissue damage in diabetes (8). COVID-19 infection disrupts glucose regulation, rendering glycemic control difficult and necessitating particularly careful management in patients with diabetes (9). Moreover, early indicators and comparison with the previous severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak (10) suggest that survivors may face sequelae, which will require long-term care. Currently, the U.S. and some other countries are experiencing surges in COVID-19 cases (1). This article will review the current state of knowledge of COVID-19 and diabetes to address nine critical questions, some of which remain unanswered (Fig. 1).

Review Methodology

We initially performed our literature search on PubMed without any filters on publication date and completed it by 10 July 2020. The search keywords varied by section. For the diabetes and comorbidities section, we searched "COVID-19" or "SARS-CoV-2" with "clinical characteristics," "clinical cohort," "clinical," or "cohort," and prioritized clinical, high-quality medical studies. We did not generally include meta-analyses and excluded preprints, since we had sufficient peer-reviewed material. To the best of our ability, we selected studies that appeared to report different patient cohorts, considering some cohorts may

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- **Are there any differences in risk to serious COVID-19 infection or death in type 1 and type 2 diabetes patients? One study does suggest greater risk in type 1 diabetes, but needs validation.**
- **Is prediabetes a risk for serious COVID-19 infection or death?**
- **Why are children at lower risk of serious COVID-19 infection or death compared to adults? And why are some children susceptible? Is the link of comorbidities, including diabetes, to critical illness applicable in children?**
- **Is gestational diabetes not a risk for serious COVID-19 infection or death as the current evidence suggests? If validated by other studies, why is this the case?**
- **Why are some races/ethnicities risks for serious infection COVID-19 or death? What role does diabetes play in this risk?**
- **Does preexisting tissue damage from diabetic complications predispose to acute COVID-19-induced organ damage and overall poorer outcomes?**
- **Why do diabetes patients exhibit a more inflammatory phenotype than non-diabetes patients with COVID-19? Does COVID-19 superimpose on preexisting diabetes inflammation?**
- **Do diabetic COVID-19 survivors face a higher chance of long term sequelae?**
- **Is COVID-19 contributing to new onset diabetes? One study suggests this might occur.**

Figure 1—Outstanding questions on diabetes in the context of COVID-19.

have been duplicated without reporting it (11). However, we may have included studies from the same cohort if the study focus was different. We focused on China, U.S., and Europe as the early epicenters. We also repeated the search with the keyword "diabetes," "acute kidney injury," or "acute cardiac injury." We read all abstracts to select relevant manuscripts, which we searched for the term "diabetes" and all relevant information. During the revision process, we updated the review with relevant literature (same criteria) published up until 18 August. For the pediatric section, we searched "COVID-19" or "SARS-CoV-2" and "diabetes" with "pediatric," "childhood," "children," "youth," or "adolescent." For the pregnancy section, we searched "COVID-19" or "SARS-CoV-2" and "diabetes" with "pregnant," "pregnancy," or "gestational." For the race section, we searched "COVID-19" or "SARS-CoV-2" and "race," "black," "African American," "Hispanic," or "Asian" and prioritized high-quality clinical studies. We also performed a subsearch using "diabetes."

Diabetes and COVID-19

General COVID-19 Patient Cohorts

Although the COVID-19 pandemic evolved quickly, there were clear early warning signs that comorbidities, including diabetes, predisposed patients to adverse outcomes (Table 1). The first reports that emerged from Wuhan, China, documented that diabetes raised the risk of dangerous infection-induced adverse outcomes and complications, leading to acute respiratory distress syndrome (ARDS), intensive care unit (ICU) admission, mechanical ventilation use, and greater risk of death (12,13). In univariate logistic regression analysis, diabetes had an odds ratio (OR) of 2.85 for in-hospital death (13). At the national level, several China studies found association of diabetes with severe disease (ICU, mechanical ventilation) (14) and death (14,15).

These findings are replicated in the U.S., where diabetes is one of the three most common comorbid conditions nationwide, with total comorbidity prevalence as high as 78% among ICU COVID-19 admissions (n = 457 total) (16). In New York City (NYC), patients with diabetes were more likely to need mechanical ventilation or ICU admission (17,18). In a different NYC cohort, the diabetes univariate hazard ratio (HR) for in-hospital mortality was 1.65, which did not persist in multivariate analysis after adjustment for age, sex, and seven additional parameters (5). In Detroit (n = 463), diabetes was more frequent in hospitalized versus discharged and ICU versus non-ICU patients but was not a risk in multivariate analysis (19). Diabetes was an independent risk for hospital admission (OR 2.24, with full adjustment for patient characteristics and comorbidities) but not for critical disease or death in a large NYC cohort (n = 5,279) (20).

In other countries, a German study (n = 50) found no differences in diabetes frequency in ARDS versus non-ARDS patients (21), though these outcomes contrast with those of another study in China (22). An observational U.K. study (n = 1,157) found that diabetes had an age- and sex-adjusted HR of 1.42 for critical care and could be integrated into a 12-point prognostic risk score (critical care admission, death) (23), similar to another 10-variable risk score (24). Collectively, these general cohort studies suggest that patients with diabetes have a higher likelihood of adverse outcomes, although other mitigating risk factors likely exist, contributing to the varying conclusions.

Cohorts of Patients With COVID-19 and Diabetes

Several reports have focused specifically on cohorts of patients with diabetes. The multicenter French Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO)

Table 1—Overview of adult COVID-19 clinical cohorts

Study	Location	Participants (*n*)	Diabetes findings	Comorbidities findings*	Select laboratory findings**
Wang et al. (12)	Wuhan, China	138	Patients with diabetes constituted 22.2% of ICU patients vs. 5.9% of non-ICU patients, $P = 0.009$	CVD, hypertension, cerebrovascular disease predisposed to ICU	Elevated WBC, neutrophils, ALT, AST, CK-MB, Cr, D-dimer, hs-TnI, LDH, PCT, and lymphopenia in ICU vs. non-ICU patients
Zhou et al. (13)	Wuhan, China	191	Patients with diabetes constituted 31% of nonsurvivors vs. 14% of survivors ($P = 0.0051$); OR 2.85 (95% CI 1.35–6.05; $P = 0.0062$) for in-hospital death in a univariate model	CVD, 24% nonsurvivors vs. 1% survivors ($P < 0.0001$), OR 21.40 (95% CI 4.64–98.76; $P < 0.0001$) in univariate model; hypertension, 48% nonsurvivors vs. 23% survivors ($P = 0.0008$), OR 3.05 (95% CI 1.57–5.92; $P = 0.0010$) in univariate model	Elevated WBC, ALT, CK, Cr, D-dimer, ferritin, hs-TnI, IL-6, LDH, PT, and PCT had significant HR >1 for death in univariate model; D-dimer had significant HR >1 for death in multivariate model
Guan et al. (14)	China	1,099	16.2% of patients with severe vs. 5.7% with nonsevere COVID-19 infections had diabetes, and 26.9% that met vs. 6.1% that did not meet the primary composite end point (ICU, mechanical ventilation use, death) had diabetes; no *P* values	5.8% of severe vs. 1.8% of nonsevere COVID-19 patients had CHD, and 9.0% that met vs. 2.0% that did not meet the primary composite end point had CHD; 23.7% of severe vs. 13.4% of nonsevere COVID-19 patients had hypertension, and 35.8% that met vs. 13.7% that did not meet the primary composite end point had hypertension; no *P* values	Elevated WBC, ALT, AST, CRP, D-dimer, LDH, PCT, and lymphopenia in severe vs. nonsevere infection and in patients that met vs. did not meet the primary composite end point, no *P* values
Wu and McGoogan (15)	China	72,314 total, 44,672 confirmed (factored into CFR)	CFR 7.3% in patients with diabetes vs. 2.3% for the entire cohort	CFR 10.5% for CVD, 6.0% for hypertension	Not examined
Richardson et al. (17)	NYC area	5,700	Diabetes one of three most common morbidities. Patients with diabetes more likely to need mechanical ventilation or ICU	Hypertension and obesity two of three most common morbidities. Hypertensive patients less likely to need mechanical ventilation or ICU; 88% of COVID-19 patients had two or more comorbidities compared with one (6.3%) or none (6.1%).	Elevated ALT, AST, BNP, CRP, D-dimer, ferritin, LDH, PCT, and lymphopenia in hospitalized COVID-19 patients
Goyal et al. (18)	NYC	393	Diabetes was more frequent in patients requiring mechanical ventilation (27.7%) vs. not (24.0%) (*P* value not stated)	Hypertension, CAD, and obesity were more frequent in patients requiring mechanical ventilation (*P* values not stated)	Majority of patients had lymphopenia (90.0%), thrombocytopenia (27%); many had elevated liver function values and inflammatory markers (CRP, D-dimer, ferritin, PCT), which were further increased in patients requiring mechanical ventilation
Cummings et al. (5)	NYC	1,150	Diabetes one of three most common morbidities. Univariate HR 1.65 (95% CI 1.11–2.44), not significant in multivariate HR 1.31 (95% CI 0.81–2.10) for in-hospital mortality	Hypertension and obesity two of three most common morbidities. Hypertension univariate HR 2.24 (95% CI 1.40–3.59); CCD univariate HR 2.21 (95% CI 1.44–3.39), multivariate HR 1.76 (95% CI 1.08–2.86); BMI $\geq$40 kg/m^2 not significant univariate HR 0.76 (95% CI 0.40–1.47) for in-hospital mortality; CKD was not a risk for in-hospital death	Aside from other altered markers, IL-6 univariate HR 1.12 (95% CI 1.04–1.21) and multivariate HR 1.11 (95% CI 1.02–1.20) and D-dimer univariate HR 1.18 (95% CI 1.10–1.27) and multivariate HR 1.10 (95% CI 1.01–1.19) for in-hospital mortality

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Table 1—Continued

Study	Location	Participants (*n*)	Diabetes findings	Comorbidities findings*	Select laboratory findings**
Suleyman et al. (19)	Detroit, MI	463	Diabetes was more frequent in hospitalized (43.4%) vs. discharged (20.4%) patients ($P < 0.001$). It was also more frequent in ICU (51.8%) vs. non-ICU (38.8%) patients ($P = 0.02$) but was not a risk in multivariate analysis for ICU or mechanical ventilation. African American race was not more frequent in admitted or ICU vs. discharged patients or a risk for mechanical ventilation or death	Hypertension, CVD, obesity, and CKD were more frequent in hospitalized vs. discharged patients. Hypertension and CKD were also more frequent in ICU vs. non-ICU patients. CKD and severe obesity were risks in multivariate analysis for ICU or mechanical ventilation	Elevated AST, Cr, and hs-TnI; lower WBC; and lymphopenia in hospitalized vs. discharged patients by univariate analysis. Elevated WBC, AST, Cr, D-dimer, ferritin, hs-TnI, LDH, PCT, and lymphopenia in ICU vs. non-ICU patients by univariate analysis
Petrilli et al. (20)	NYC	5,279	Diabetes had multivariate OR 2.24 (95% CI 1.84–2.73; $P < 0.001$) for hospital admission, with adjustment for patient characteristics, comorbidities	All multivariate: heart failure OR 4.43 (95% CI 2.59–8.04; $P < 0.001$), hypertension OR 1.78 (95% CI 1.49–2.12; $P < 0.001$), CKD OR 2.6 (95% CI 1.89–3.61; $P < 0.001$), hyperlipidemia OR 0.62 (95% CI 0.52–0.74; $P < 0.001$), BMI 25.0–29.9 kg/m^2 (overweight) OR 1.3 (95% CI 1.07–1.57; $P = 0.007$), BMI 30–39.9 kg/m^2 (obese class I and II) OR 1.8 (95% CI 1.47–2.2; $P < 0.001$), BMI ≥40 kg/m^2 (obese class III) OR 2.45 (95% CI 1.78–3.36; $P < 0.001$); all for hospital admission, adjusted for same variables as diabetes	Elevated Cr, CRP, D-dimer, PCT, troponin, and lymphopenia in critical COVID-19
Dreher et al. (21)	Aachen, Germany	50	Diabetes did not raise the risk for ARDS; no *P* values	Obesity, but not hypertension, raised the risk for ARDS; no *P* values	Elevated WBC, CK, CRP, D-dimer, IL-6, LDH, and PCT; no *P* values
Wu et al. (22)	Wuhan, China	201	Diabetes was more frequent in ARDS (19.0%) than non-ARDS (5.1%) patients ($P = 0.002$); risk for ARDS (HR 2.34 [95% CI 1.35–4.05]; $P = 0.002$) but not death (HR 1.58 [95% CI 0.80–3.13]; $P = 0.19$)	Hypertension was more frequent in ARDS (27.4%) than non-ARDS (13.7%) patients ($P = 0.02$), risk for ARDS (HR 1.82 [95% CI 1.13–2.95]; $P = 0.01$) but not death (HR 1.70 [95% CI 0.92–3.14]; $P = 0.09$)	Elevated neutrophils, AST, CRP, D-dimer, ferritin, LDH, and PT had significant HR >1 for ARDS; neutrophils, D-dimer, IL-6, and LDH had significant HR >1 for death
Galloway et al. (23)	U.K.	1,157	Diabetes had HR (adjustment for sex, age) of 1.42 for critical care (95% CI 1.04–1.95; $P = 0.029$)	Hypertension had HR (adjusted for sex, age) of 1.53 for critical care or death (95% CI 1.24–1.90; $P = 0.000$)	Neutrophils, Cr, and CRP had significant HR >1 for critical care or death
Liang et al. (24)	China	1,590, discovery cohort; 710, validation cohort; risk score for critical illness	6.8% noncritical vs. 23.7% critical disease among patients with diabetes	3.2% noncritical vs. 9.9% critical disease among CVD patients; 14.8% noncritical vs. 40.5% critical disease among hypertension patients. Number of comorbidities had OR 1.60 (95% CI 1.27–2.00; $P < 0.001$) in multivariate analysis	Aside from other altered markers, neutrophil-to-lymphocyte ratio (OR 1.06 [95% CI 1.02–1.10]; $P = 0.003$) and LDH (OR 1.002 [95% CI 1.001–1.004]; $P < 0.001$) integrated into a 10-point risk score for critical illness
Cariou et al. (25)	France	1,317, of whom 1,166 with T2D	Diabetes type, HbA_{1c}, glucose-lowering therapy use did not affect primary outcome (mechanical ventilation and/or death within 7 days of admission) in univariate analysis	Micro- (OR 2.14 [95% CI 1.16–3.94]; $P = 0.0153$) and macrovascular (OR 2.54 [95% CI 1.44–4.50]; $P = 0.0013$) complications independently associated with 7-day mortality; BMI multivariate OR 1.28 (95% CI 1.10–1.47), $P < 0.0010$ for composite	AST (OR 2.23 [95% CI 1.70–2.93]; $P < 0.0001$) and CRP (OR 1.93 [95% CI 1.43–2.59]; $P < 0.0001$) independently associated with primary outcome; higher lymphocytes were protective (OR 0.67 [95% CI 0.50–0.88]; $P = 0.0050$)

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Table 1—Continued

Study	Location	Participants (*n*)	Diabetes findings	Comorbidities findings*	Select laboratory findings**
Barron et al. (26)	U.K.	23,698 COVID-19 deaths, 364 T1D COVID-19 deaths, 7,434 T2D COVID-19 deaths	T1D OR 2.86 (95% CI 2.58–3.18; $P < 0.001$) and T2D OR 1.80 (95% CI 1.75–1.86; $P < 0.001$) for death, with adjustment for age, sex, deprivation, ethnicity, CVD, cerebrovascular disease	CVD and cerebrovascular disease more frequent in T1D and T2D vs. nondiabetes in COVID-19 deaths	Not examined
Zhang et al. (27)	Wuhan, China	258, of whom 63 with diabetes	Diabetes had multivariate HR 3.64 (95% CI 1.09–12.21; $P = 0.036$); elevated FBG (>7.54 mmol) had multivariate HR 1.19 (95% CI 1.08–1.31; $P < 0.001$); both for death adjusted for age, CVD, CKD, inflammatory markers	CVD more frequent in patients with diabetes (23.8%) vs. patients without diabetes (12.3%), $P = 0.027$; CKD more frequent in patients with diabetes (8.8%) vs. patients without patients (2.1%), $P = 0.027$	Elevated WBC, neutrophils, CK-MB, D-dimer, TT in patients with diabetes vs. patients without diabetes
Guo et al. (28)	Wuhan, China	174, overall analysis; 50, subgroup analysis	Patients with diabetes without any other comorbidities (16.5%) died more often than patients without diabetes without comorbidities (0%) ($P = 0.03$); however, the latter patients were younger	CVD was more prevalent in patients with diabetes, $P = 0.013$	Elevated neutrophils, D-dimer, and ESR, and lymphopenia in patients with diabetes vs. patients without diabetes; neutrophils, ALT, CRP, D-dimer, ESR, ferritin, IL-6, LDH, and lymphopenia in patients with diabetes vs. patients without diabetes without comorbidities; however, the latter patients were younger
Zhu et al. (3)	Hubei Province, China	7,337, of whom 952 with T2D	T2D patients had higher mortality: 7.8% vs. 2.7% overall, adjusted HR 1.49 (95% CI 1.13–1.96; $P = 0.005$); well-controlled blood glucose confers lower all-cause mortality, adjusted HR 0.14 (95% CI 0.03–0.60; $P = 0.008$)	Blood glucose correlated with comorbid CHD, hypertension	T2D patients had elevated WBC, neutrophils, Cr, CRP, D-dimer, IL-6, LDH, PCT, and lymphopenia vs. patients without diabetes; T2D patients with well-controlled vs. poorly controlled blood glucose had significantly fewer incidences of elevated WBC, neutrophils, ALT, AST, Cr, CRP, D-dimer, PCT, and lymphopenia; no *P* values
Iacobellis et al. (29)	Miami, FL	85	Admission hyperglycemia best predicted poor chest radiological outcomes	BMI correlated with poor chest radiological outcomes	Not examined
Li et al. (30)	Wuhan, China	132, of whom 130 with T2D	Patients with diabetes stratified by admission glucose: group 1 (≤11 mmol/L) vs. group 2 (>11 mmol/L); group 2 had longer diabetes duration, more likely to suffer ACI, ICU admission, death	No difference in comorbidities in group 1 vs. group 2	Elevated WBC, CRP, D-dimer, ESR, IL-6, and lymphopenia in group 2 vs. group 1; WBC ($>10^9$/L), Cr (<57/0 μmol/L), D-dimer (≥1.5 μg/L), hs-TnI (>26.2 pg/mL), LDH (>245 units/L), PCT univariate OR >1 for in-hospital complications
Chao et al. (31)	Taiwan	452	High glucose variability within the first day of ICU admission correlated with 30-day mortality, particularly in patients without diabetes. High glucose variability was more frequent in patients with diabetes	Except for diabetes, no difference in other comorbidities (e.g., CKD, CHD, cerebrovascular disease) in patients with high vs. low glucose variability; APACHE II score independently correlated with higher 30-day mortality	No differences in Cr, CRP, and PCT in patients with high vs. low glucose variability

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Table 1—Continued

Study	Location	Participants (*n*)	Diabetes findings	Comorbidities findings*	Select laboratory findings**
Bode et al. (32)	U.S.	1,122	Diabetes and/or uncontrolled hyperglycemia increased hospital length of stay and mortality	Kidney function, as assessed by eGFR, was lower in patients with diabetes and/or uncontrolled hyperglycemia at admission	Elevated Cr in patients with diabetes and/or uncontrolled hyperglycemia vs. patients without diabetes or with controlled blood glucose patients
Williamson et al. (4)	U.K.	10,926 COVID-19 deaths vs. 17,278,392 control subjects	Diabetes with HbA_{1c} <7.5% (58 mmol/mol), HR 1.31 (95% CI 1.24–1.37), and with HbA_{1c} ≥7.5% (58 mmol/mol), HR 1.95 (95% CI 1.83–2.07), for death, adjusted for age, sex, comorbidities, smoking, socioeconomic status. Mixed race, HR 1.43 (95% CI 1.11–1.85); South Asian, HR 1.44 (95% CI 1.32–1.58); and Black, HR 1.48 (95% CI 1.30–1.69); risks for death after adjustment for the same variables	BMI 30–34.9 kg/m^2 (obese class I) nonsignificant HR 1.05 (95% CI 1.00–1.11), BMI 35–39.9 kg/m^2 (obese class II) HR 1.40 (95% CI 1.30–1.52), BMI ≥40 kg/m^2 (obese class III) HR 1.92 (95% CI 1.72–2.13), hypertension HR 0.89 (95% CI 0.85–0.93), CHD HR 1.17 (95% CI 1.12–1.22), reduced kidney function eGFR 30–60 mL/min/1.73 m^2 HR 1.33 (95% CI 1.28–1.40), eGFR <30 mL/min/1.73 m^2 HR 2.52 (95% CI 2.33–2.72), stroke/dementia HR 2.16 (95% CI 2.06–2.27), for death, adjusted for the same parameters as diabetes	Not examined
Holman et al. (33)	U.K.	464 T1D COVID-19 deaths, 10,525 T2D COVID-19 deaths	T1D: HbA_{1c} ≥10.0% (86 mmol/mol) HR 2.23, T2D: HbA_{1c} 7.5–8.9% (59–74 mmol/mol) HR 1.22 (95% CI 1.15–1.30), HbA_{1c} 9.0–9.9% (75–85 mmol/mol) HR 1.36 (95% CI 1.24–1.50), HbA_{1c} ≥10.0% (86 mmol/mol) HR 1.61 (95% CI 1.47–1.77); all $P < 0.0001$, adjusted for age, sex, deprivation, ethnicity, clinical, CVD, CKD, among others	T1D: inverse relation of eGFR with HR; U-shape relation of BMI with HR, reference to overweight category (BMI 25.0–29.9 kg/m^2); CVD HR>1, no significance of hypertension and cholesterol. T2D had the same risks, plus hypertension HR <1	Not examined
Zhang et al. (34)	Wuhan, China	166	Diabetes and hyperglycemia secondary to COVID-19 increase the risk of critical disease (32.8% and 38.1%, respectively, vs. 9.5% overall, $P < 0.05$ for both) and composite outcome (ICU, mechanical ventilation use, death)	Hypertension was frequent in patients with diabetes and secondary hyperglycemia ($P = 0.029$)	Elevated WBC, neutrophils, ALT, AST, CRP, D-dimer, ESR, ferritin, IL-8, LDH, and N-terminal pro-BNP in COVID-19 patients with diabetes and hyperglycemia secondary vs. without diabetes and with normoglycemia
Wang et al. (35)	Wuhan, China	605	Admission FBG ≥7.0 mmol/L multivariate HR 2.30 (95% CI 1.49–3.55; $P = 0.0002$) for 28-day mortality; admission FBG ≥7.0 and 6.1–6.9 vs. <6.1 mmol/L OR 3.99 (95% CI 2.71–5.88) and 2.61 (95% CI 1.64–4.41), respectively, for 28-day in-hospital complications	Hypertension and CHD had no significant effect on 28-day mortality; CKD and cerebrovascular disease had univariate HR >1 for 28-day mortality	Not examined
Smith et al. (36)	NJ	184	Most patients had diabetes (62.0%) or prediabetes (23.9%); intubated patients had higher FBG ($P = 0.013$) and HbA_{1c} ($P = 0.034$) vs. nonintubated	Most common preexisting conditions: hypertension (60.3%), hyperlipidemia (33.7%), dementia (13.0%), CKD (13.0%), CAD (12.0%), and CHD (10.9%); intubated patients had higher BMI ($P = 0.030$) vs. nonintubated	Not examined

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Table 1—Continued

Study	Location	Participants (*n*)	Diabetes findings	Comorbidities findings*	Select laboratory findings**
Simonnet et al. (39)	Lille, France	124	Diabetes was not a risk factor in univariate logistic regression analysis	Obesity (≥35 kg/m^2 BMI) univariate OR 6.75 (95% CI 1.76–25.85; $P = 0.015$), multivariate OR 7.36 (95% CI 1.63–33.14; $P = 0.021$); hypertension univariate OR 2.81 (95% CI 1.25–6.3; $P = 0.012$) but not significant in multivariate analysis; dyslipidemia was not a risk factor in univariate logistic regression analysis	Not examined
Gao et al. (41)	Wenzhou, China	150	Diabetes more prevalent in obese (24.0%) vs. nonobese (14.7%) COVID-19 patients	Obesity had OR 3.00 (95% CI 1.22–7.38) after adjustment for age, sex, smoking status, hypertension, diabetes, dyslipidemia	Elevated CRP and lymphopenia in obese vs. nonobese COVID-19 patients
Shi et al. (43)	Wuhan, China	1,561, of whom 153 with diabetes analyzed vs. 153 age- and sex-matched 153 patients without diabetes	Diabetes (multivariate HR 1.58 [95% CI 0.84–2.99]) not an independent risk for in-hospital death; patients with diabetes likelier to be admitted to ICU and experience complications (ACI, AKI, ARDS, etc.) and death; nonsurvivor patients with diabetes likelier to have hypertension and CVD ($P < 0.05$); hypertension multivariate HR 3.10 (95% CI 1.14–8.44) for in-hospital death of patients with diabetes	Hypertension multivariate HR 2.50 (95% CI 1.30–4.78) and CVD multivariate HR 2.24 (95% CI 1.19–4.23) associated with in-hospital death	Elevated PCT and lower CD8$^+$ T cells in patients with diabetes vs. patients without diabetes; elevated glucose, HbA_{1c}, WBC, neutrophils, Cr, CRP, D-dimer, PCT, PT, and lymphopenia and lower eGFR, CD3$^+$, CD4$^+$, CD8$^+$, CD19$^+$, and CD16$^+$56$^+$ cells in nonsurvivor vs. survivor patients with diabetes
Lassale et al. (40)	U.K.	640 COVID-19 hospitalizations from 340,966 registrants in UK Biobank subset from 900 COVID-19 hospitalizations and 428,494 registrants	Diabetes more prevalent and HbA_{1c} higher in hospitalized vs. nonhospitalized patients (full data set), $P < 0.001$; Log HbA_{1c} remained associated in multivariate analysis (OR 1.60 [95% CI 1.02–2.52]; $P = 0.043$; sub–data set); diabetes more prevalent in Black and Asian patients (full data set)	CVD, hypertension, BMI, WHR higher and cholesterol, HDL-c lower in hospitalized vs. nonhospitalized patients (full data set), $P < 0.001$; BMI, WHR, cholesterol remained significant in multivariate analysis; Black patients (OR 2.66 [95% CI 1.82–3.91]; $P < 0.001$) more susceptible to hospitalization, with adjustment for age, sex, comorbidities, and socioeconomic factors	Elevated CRP in hospitalized vs. nonhospitalized COVID-19 patients but did not remain significant in multivariate analysis
Price-Haywood et al. (45)	LA	3,481	18.5% of Black patients had diabetes vs. 10.9% White. No analysis performed to disease severity. Black race was a hospitalization risk but not an independent in-hospital mortality risk	Charlson Comorbidity Index score OR 1.05 (95% CI 1.00–1.10) for hospitalization (accounting for race, age, sex, low-income area of residence, insurance plan, obesity) but HR 0.99 (95% CI 0.94–1.03) for in-hospital death; hypertension and CKD more prevalent in Black vs. White patients	Aside from other altered markers, AST, Cr, CRP, PCT, and lymphopenia had significant HR >1 for in-hospital death, after adjustment for race, age, sex, comorbidities, low-income area of residence, and laboratory measures

ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; BNP, brain natriuretic peptide; CAD, coronary artery disease; CCD, chronic cardiac disease; CFR, case fatality rate; CHD, coronary heart disease; CK, creatine kinase; CK-MB, creatine kinase, muscle and brain type; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-c, high-density lipoprotein cholesterol; IL-6, interleukin 6; PT, prothrombin time; T1D, type 1 diabetes; T2D, type 2 diabetes; TT, thrombin time. *Conditions comorbid with diabetes considered. **Select laboratory findings for significant differences reported in immune cell populations, cytokines, and biomarkers of infection and kidney, liver, and cardiac damage. Changes were reported if there were significant differences in either mean values or in the number of patients above a cutoff value.

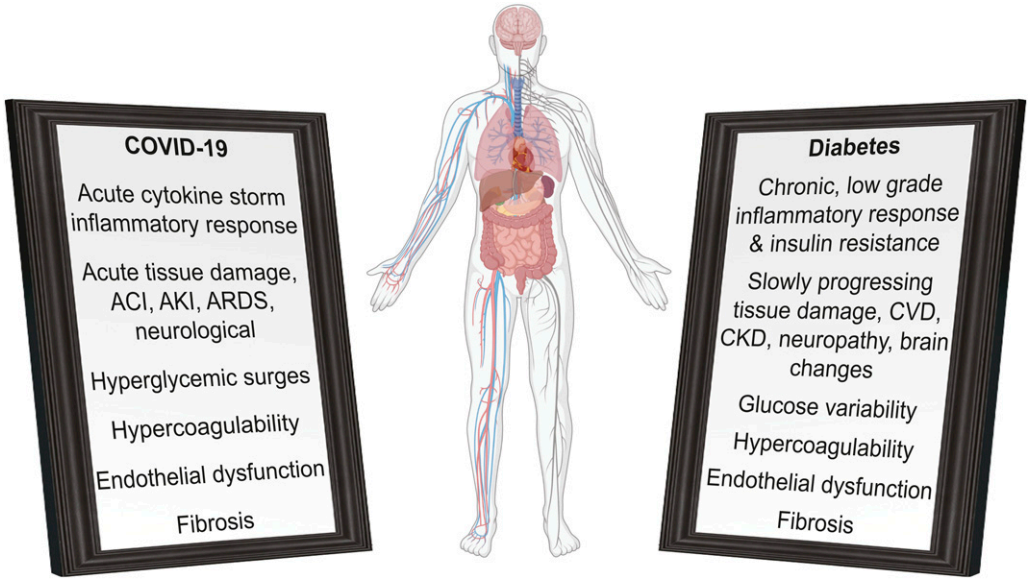

Figure 2—Illustration of parallels in acute COVID-19 pathology versus chronic diabetes pathology. COVID-19 infection induces acute inflammatory cytokine storm, hyperglycemic surges, and acute organ damage. Diabetes is characterized by chronic, low-grade inflammation, glucose variability, and slowly progressing tissue damage in microvascular (CKD, neuropathy, brain) and macrovascular (CVD) complications. Additional shared detrimental mechanisms include hypercoagulation, endothelial dysfunction, and fibrosis. Drawn in part with BioRender.

study (n = 1,317 participants with diabetes, 88.5% of whom had type 2 diabetes) observed that diabetes type and glycated hemoglobin (HbA_{1c}) level did not affect the primary outcome in univariate analysis, i.e., tracheal intubation for mechanical ventilation and/or death within 7 days of admission (25). Another large study, led by the National Health Service (NHS) England, also focused on both type 1 (n = 364) and type 2 (n = 7,434) diabetes–associated COVID-19 deaths and determined multivariate ORs of 2.86 and 1.80, respectively, with adjustment for age, sex, ethnicity, deprivation, CVD, and cerebrovascular disease, though they could not adjust for other frequent comorbidities, hypertension, chronic kidney disease (CKD), and BMI, due to data set limitations (26). Notably, most studies have not differentiated diabetes type; CORONADO found no differences between type 1 and type 2 diabetes in COVID-19 outcomes, but there were only 39 patients with type 1 diabetes. In contrast, the NHS England study might suggest that patients with type 1 diabetes are at greater risk, though this remains to be validated by additional studies (Fig. 1).

A study from China with 258 COVID-19 patients, of whom 63 had diabetes, reported diabetes had a multivariate HR of 3.64 for death, with adjustment for age, comorbidities, and inflammatory markers (27). Guo et al. (28) accounted for comorbidities by comparing mortality in patients without diabetes (0%) versus with diabetes (16.5%) without comorbidities; however, they failed to consider age, which significantly differed between groups. In a study of COVID-19 patients with type 2 diabetes, diabetes led to a higher all-cause mortality of 7.8% (vs. 2.7%), with HR 1.49, with adjustment for age, sex, and infection severity (3). These studies of cohorts with diabetes confirm the concept that persons with diabetes who contract COVID-19 disease have poorer outcomes.

Glycemic Control and Elevated Fasting Blood Glucose

Well-controlled blood glucose has emerged as an important outcome parameter and conferred lower mortality (HR 0.14) in a propensity score–matching model that accounted for age, sex, comorbidities, and several additional parameters (3). This finding agrees with other studies that identified diabetes and/or uncontrolled or variable hyperglycemia at admission (29,30), ICU admission (31), or during in-hospital stay (32) as a severe disease or mortality risk. In the large U.K. OpenSAFELY study of 10,926 COVID-19 deaths in comparison with a database of 17,278,392 adults, greater mortality occurred with poorer glycemic control (stratified by HbA_{1c}) (4). Patients with diabetes with HbA_{1c} <7.5% had a fully adjusted HR of 1.31 for death, whereas HR was 1.95 with HbA_{1c} ≥7.5%. These findings were mirrored by the NHS England study in both patients with type 1 diabetes (HbA_{1c} ≥10.0%, HR 2.23) and patients with type 2 diabetes (HbA_{1c} 7.5–8.9%, HR 1.22; HbA_{1c} 9.0–9.9%, HR 1.36; and HbA_{1c} ≥10.0%, HR 1.61) (33).

COVID-19 can also induce hyperglycemia in patients without diabetes, secondary to infection, which increases the risk of critical disease (34,35). Finally, prediabetes, characterized by elevated fasting blood glucose or impaired insulin sensitivity, has been mostly overlooked in COVID-19 studies but could nevertheless pose a threat to clinical outcomes (Fig. 1). In a U.S. study of 184 patients, most had diabetes (62.0%) or prediabetes (23.9%), and stratifying patients solely by elevated fasting blood glucose or HbA_{1c} increased the risk of intubation (36). A China study also found that elevated fasting blood glucose (>7.54 mmol cutoff) independently predicted mortality (HR 1.19) (27).

Overall, there is a consensus from clinical studies and meta-analyses (36 and reviewed in 37) that diabetes is a risk factor for serious COVID-19 infection and mortality, though this dependency may be less significant by multivariate analysis in some studies. Varying study results are likely due to the fact that many, but not all, patients with diabetes suffer from additional comorbidities, such as obesity, hypertension, and CVD, which are independent risk factors (Fig. 1).

Comorbidities and COVID-19

Comorbidities in General COVID-19 Patient Cohorts

Obesity (19,20,25,39–41), CKD (19,20), CVD (5,20), and hypertension (20) persist as risk factors for hospitalization or serious COVID-19 disease in multivariate analysis in some studies, after adjustment for various clinical variables (Table 1 and Fig. 1), and in meta-analyses (37). In a French cohort ($n = 124$), obesity (BMI $\geq$35 kg/m^2), but not diabetes, was a strong predictor for mechanical ventilation use, with multivariate OR 7.36, after adjustment for age, sex, diabetes, and hypertension (39). The OpenSAFELY study reported that mortality risk increased with BMI, with HR 1.40 for class II obesity (BMI 35–39.9 kg/m^2) and HR 1.92 for class III obesity (BMI $\geq$40 kg/m^2) (4). This was similar to a NYC study, where BMI proportionately increased hospitalization risk (20). In a China cohort ($n = 150$), obesity was an independent predictor of serious infection (multivariate OR 3.0) and obese patients were likelier to have diabetes versus other age- and sex-matched COVID-19 patients, underscoring the frequent occurrence of comorbidities in patients with diabetes (41). Surprisingly, obesity with BMI $\geq$40 kg/m^2 was not a risk for in-hospital mortality in a NYC cohort (5).

There are fewer reports on comorbid dyslipidemia. The most comprehensive analysis leveraged data from the UK Biobank as a control population ($n = 428,494$) versus hospitalized COVID-19 patients ($n = 900$) (40). Diabetes, HbA_{1c}, CVD, hypertension, BMI, and waist-hip-ratio (WHR) were higher and cholesterol and HDL cholesterol lower in COVID-19 patients. Log(HbA_{1c}), BMI, and WHR (OR > 1) and total cholesterol (OR < 1) remained significant in multivariate analysis in a subset of 340,966 UK Biobank registrants vs. 640 COVID-19 hospitalized patients. Finally, LDL did not vary significantly between patients with diabetes with poorly or well-controlled glucose (3) and was protective from ARDS (HR 0.63) but not death (22).

Comorbidities in Cohorts of Patients With COVID-19 and Diabetes

Patients with diabetes frequently suffer from comorbidities, e.g., obesity, dyslipidemia, hypertension, CVD, and CKD (42), which would predispose them to poorer COVID-19 outcomes. In mostly CORONADO participants with type 2 diabetes, obesity by BMI positively predicted the study primary outcome, with OR 1.28 (i.e., tracheal intubation and/or death within 7 days of admission) (25). Dyslipidemia, although present in 51.0% of patients, did not significantly increase risk of the composite primary outcome (25). In a second NHS England study, those who died from COVID-19 (type 1 diabetes, $n = 464$; type 2 diabetes, $n = 10,525$) were compared with individuals with diabetes registered to a practice (type 1, $n = 264,390$; type 2, $n = 2,874,020$) to identify mortality risk factors (33). Type 1 diabetes shared the same risks as type 2 diabetes for COVID-19 mortality, with preexisting CVD, CKD, and obesity identified as independent factors. One study, with COVID-19 patients with diabetes ($n = 153$) age and sex matched to 153 COVID-19 patients without diabetes reported that CVD and hypertension were independent risk factors for mortality risks among all patients (43). These studies support the idea that comorbidities in patients with diabetes, independent of diabetes itself, increase adverse COVID-19 disease outcomes.

Cumulative Comorbidities Effect

Furthermore, COVID-19 patients with more than one comorbidity may be especially vulnerable. In NYC, COVID-19 patients were far likelier to have two or more comorbidities, constituting 88% of hospital admissions versus admissions of patients with only one comorbidity (6.3%) or no comorbidities (6.1%) (17). In a nationwide study in China ($n = 1,590$), the HR was 1.79 for one comorbidity and as high as 2.59 for two or more comorbidities after adjustment for age and smoking status (44). When the data from this cohort were used to develop a scoring system to predict serious clinical trajectories from admission status, the number of comorbidities (OR 1.60) emerged as 1 of 10 variables (24). The Charlson Comorbidity Index, a score based on the presence of comorbidities from a list that includes diabetes and kidney and cardiac diseases, had a multivariate OR of 1.05 for hospitalization but an HR of only 0.99 for in-hospital death (45).

Overall, in assessment of risk for a COVID-19 patient with diabetes at admission, overall comorbidities, including degree of glucose control (assessed by HbA_{1c} [36,40]), fasting blood glucose (36), obesity (19,25,39,40), and the number of additional comorbid conditions, will be important clinical parameters to consider (Fig. 1).

Pediatric Diabetes and Comorbidities in COVID-19

Fortunately, there is agreement to date that most pediatric COVID-19 patients present with asymptotic or mild disease (46). Nevertheless, some children suffer from more serious COVID-19 infection, requiring hospitalization and even pediatric ICU (PICU) (Table 2). The reasons for serious illness remain incompletely understood; however, drawing a parallel to adults, the presence of comorbidities, which are less frequent in young patients, may be one reason fewer children are vulnerable to COVID-19 but why some still fall critically ill. Given the recent rise in type 2 diabetes and obesity in youth, there could be a significant number of children at risk. Unfortunately, the few studies that have examined diabetes and other comorbidities in children with COVID-19 are relatively small, making it hard to draw conclusions.

Table 2—Overview of pediatric and pregnancy COVID-19 clinical cohorts

Study	Location	Participants (*n*)	Diabetes findings	Comorbidities findings*	Select laboratory findings**
Shekerdemian et al. (47)	U.S., Canada	48 pediatric patients admitted to PICUs	8% had diabetes	83% had significant comorbidities: 15% were obese, 6% had congenital heart disease	Not examined
Chao et al. (48)	NYC	21 pediatric outpatients, 33 to GPMU, 13 to PICU	Diabetes noted in critical illness (3 of 13) but not significantly correlated to PICU	Obesity prevalent in critical illness (3 of 13) but not significantly correlated to PICU	Lower AST and elevated CRP, PCT, and pro-BNP in PICU vs. non-PICU patients
Zachariah et al. (49)	NYC	50 hospitalized pediatric patients	Diabetes did not raise the risk of severe disease, but few patients had diabetes ($n = 3$)	Significantly more patients were obese with severe (67%) vs. nonsevere (20%) COVID-19 ($P = 0.03$)	Elevated CRP and PCT in severe vs. nonsevere COVID-19
Otto et al. (50)	U.S.	424 patients age 0–21 years, of whom 77 were hospitalized	Diabetes noted infrequently	13% of all patients were obese	Not examined
Ebekozien et al. (51)	U.S.	33 COVID-19 positive, 31 COVID-19–like T1D pediatric and adult patients	Hyperglycemia and DKA were common adverse outcomes	Obesity was prevalent; CVD, hypertension, hyperlipidemia also present	Not examined
Sentilhes et al. (52)	France	54 pregnant females	Only four had gestational diabetes mellitus; sample size too small for any potential link to COVID-19	Obesity may be a risk; only two had gestational hypertension; sample size too small for any potential link to COVID-19	Elevated ALT, AST, CRP, and lymphopenia in hospitalized COVID-19 patients
Lokken et al. (53)	WA	46 pregnant females	Only one had gestational diabetes mellitus; sample size too small for any potential link to COVID-19	26.1% had an underlying condition; two-thirds were overweight (28.6%, $n = 12$) or obese (35.7%, $n = 15$) by prepregnancy BMI; 15% developed severe disease, of whom 80% were overweight or obese by prepregnancy BMI; only two had gestational hypertension; sample size too small for any potential link to COVID-19	Not examined at population level
Knight et al. (54)	U.K.	427 pregnant females	3% had diabetes, 12% had gestational diabetes mellitus,; no analysis performed for disease severity	35% overweight, 34% obese, 34% preexisting comorbidities; no analysis performed for disease severity	Not examined
Kayem et al. (55)	France	617 pregnant females	Preexisting diabetes (2.3% prevalence in total population) raised the risk of severe disease, RR 3.8 (95% CI 1.4–10.7), but not gestational diabetes mellitus (11.5% prevalence)	BMI (RR 1.9 [95% CI 1.4–2.5]), hypertension, gestational hypertension or preeclampsia were more common in severe disease	Not examined

ALT, alanine aminotransferase; BNP, brain natriuretic peptide; CRP, C-reactive protein; DKA, diabetic ketoacidosis; GPMU, general pediatric medical unit; T1D, type 1 diabetes. *Conditions comorbid with diabetes considered. **Select laboratory findings for significant differences reported in immune cell populations, cytokines, and biomarkers of infection and kidney, liver, and cardiac damage. Changes were reported if there were significant differences in either mean values or in the number of patients above a cutoff value.

A cross-sectional study of 48 pediatric patients (0–21 years old), admitted to PICUs across the U.S. and Canada, found 83% had significant comorbidities: 15% were obese, 8% had diabetes, and 6% had congenital heart disease (47). A children's hospital in NYC ($n = 67$, aged 1 month–21 years) admitted 13 patients to PICU, noting the presence of both diabetes (3 of 13) and obesity (3 of 13) but not to significance; however, the cohort was small (48). Another study ($n = 50$, aged 6 days–21 years) at a different NYC children's tertiary care center found significantly more obesity in severe (67%) versus nonsevere (20%) COVID-19, but not diabetes, possibly due to the small number of patients with diabetes ($n = 3$) (49). Obesity is a recurrent theme and was relatively prevalent in other pediatric studies also (50,51).

The cumulative evidence from pediatric studies suggests that comorbidities may be a predisposing factor for serious COVID-19 infection in children, particularly obesity. The impact of diabetes remains unclear due to relatively low study participant numbers (Fig. 1).

Pregnancy, Diabetes, and Comorbidities in COVID-19

Pregnancy is a vulnerable period, particularly since gestational diabetes mellitus may develop; yet, few studies have examined pregnant women admitted for COVID-19 infection (Table 2). A French cohort of 54 pregnant women with suspected or confirmed COVID-19 included four patients with gestational diabetes mellitus and two with gestational hypertension, which were too few to analyze for a potential link to infection severity (52). However, prepregnancy overweight or obese BMI were relatively prevalent, which the authors concluded could be a risk factor for COVID-19 disease. Another small study ($n = 46$), in the U.S., also found a high prevalence of elevated prepregnancy BMI (28.6%, overweight, and 35.7%, obese) (53). Moreover, 15% of pregnant patients developed severe infection, of whom 80% were overweight or obese. A U.K. study of 427 pregnant women with confirmed COVID-19 drew similar observations, finding that 35% of patients were overweight and 34% were obese (54). The diabetes prevalence was 3%, whereas it was 12% for gestational diabetes mellitus, but no analysis of disease severity was performed.

The largest study to date was in 617 pregnant French women (55). Preexisting diabetes was present in 2.3% of the total population and raised the chance of severe disease, with a risk ratio (RR) of 3.8. In contrast, gestational diabetes mellitus, at 11.5% prevalence, did not affect outcomes for infection severity. The investigators did not discuss reasons for the difference in risk from preexisting diabetes versus gestational diabetes mellitus, but it raises the question of whether gestational diabetes mellitus interacts distinctly with COVID-19 pathophysiology (Fig. 1). Diabetes complications, for instance, from preexisting diabetes, could be a factor for serious infection, which draws parallels to studies of general populations with diabetes (25). The study also found that BMI has an RR of 1.9, hypertension an RR of 2.4, and gestational hypertension or preeclampsia an RR of 2.4 for severe COVID-19, though the latter two did not reach significance.

Collectively, the data from pregnancy cohorts echo findings from adult studies, with diabetes, obesity, and comorbidities likely predisposing to poorer outcomes. However, it is possible that gestational diabetes mellitus may not be a factor, though larger studies are needed for us to definitively conclude this.

Race, Diabetes, and Comorbidities in COVID-19

Race disparities are an emergent theme during the COVID-19 pandemic (Table 3). The precise reasons to date remain unclear, though the prevalence of comorbidities, including obesity, (56) and socioeconomic factors (57) have been suggested. Of the U.S. population, 18% are Hispanic, 13% Black, and 0.7% American Indian or Alaska Native; yet, these groups have disproportionately constituted 33%, 22%, and 1.3%, respectively, of adult U.S. COVID-19 cases (58) and are also highly represented in hospitalized pediatric patients (50).

Several observational studies have taken a more detailed look to understand these racial disparities. In Detroit cohorts, Black race did not increase risk of severe infection (19,59); however, diabetes or comorbidities prevalence by race was not examined (19). These findings partly agree with those of a Georgia study ($n = 297$), which found that although hospitalizations among Black patients (83.2%) were disproportionate to numbers among other races, indicating greater disease severity, Black patients did not have higher mechanical ventilation use or mortality (60). This study also reported the prevalence of comorbidities, which did not differ significantly for diabetes in Black versus other races but did differ for hypertension and mean BMI. A larger Louisiana cohort ($n = 3,481$) similarly concluded that Black race was a hospitalization risk but not an independent in-hospital mortality risk (45). Although the investigators found diabetes, hypertension, and CKD prevalence to be higher in Black versus White patients, they did not perform an analysis for disease severity. A California study ($n = 1,052$) analyzed hospitalization risk for Black, Asian, and Hispanic race relative to White, but only Black race had an OR 2.7, after adjustment for sex, age, comorbidities, and socioeconomic factors (57). U.K. studies have also noted greater susceptibility of Black patients, and other race minorities, to COVID-19 disease (61) and hospitalization (40), after adjustment for several cardiometabolic and socioeconomic factors. Strikingly, a NYC study found that Black race was protective for critical illness and death, whereas Hispanic race was a risk for hospitalization (20).

Importantly, some studies have reported increased mortality risk for Black race and other minorities. Analysis of NYC demographics and COVID-19 deaths ($n = 4,260$) revealed that Hispanic (22.8%) and Black (19.8%) patients had the highest age-adjusted mortality per 100,000, which corresponded to the highest obesity rates: 25.7% and 35.4%, respectively (56). However, the study did not adjust for other important variables. Lacking complete U.S. nationwide disaggregated data by race, Millett et al. (62) analyzed county-level demographics and COVID-19 deaths. Counties with a greater

Table 3—Overview of COVID-19 clinical cohorts with investigation of susceptibility by race and ethnicity

Study	Location	Participants (*n*)	Diabetes findings	Comorbidities findings*	Select laboratory findings**
Stokes et al. (58)	U.S.	599,636 of known race	No correlation study of diabetes to race performed	33% Hispanic, 22% Black, 1.3% American Indian or Alaska Native, which account for 18%, 13%, and 0.7% of the U.S. population, respectively, suggesting they were disproportionately affected by COVID-19	Not examined
Bhargava et al. (59)	Detroit, MI	197	Diabetes more frequent in patients with severe (48.6%) vs. nonsevere infection (30.1%), OR 2.20 (95% CI 1.21–4.0; $P = 0.009$) in univariate analysis but not multivariate; no correlation study of diabetes to race performed	Obesity, hypertension, congestive heart failure, cerebrovascular disease did not increase univariate OR of severe disease, though CKD did; 82.1% were Black, and Black race was not a risk for severe infection	Elevated Cr and PCT had significant univariate OR >1 for severe disease; elevated Cr from baseline and initial CRP had significant multivariate OR >1 for severe infection
Gold et al. (60)	GA	297; Black hospitalizations (83.2%) were disproportionate to other races, indicating greater disease severity	Diabetes prevalence did not differ significantly in Black patients (41.7%) vs. in patients of other races (32.0%) $P = 0.21$	Hypertension more common in Black patients (69.6%) vs. patients of other races (54.0%), $P = 0.047$; mean BMI higher in Black (31.4%) patients vs. patients of other races (29.6%), $P = 0.003$; Black patients did not have higher mechanical ventilation use or mortality	Not examined
Azar et al. (57)	CA	1,052 confirmed cases	Diabetes had OR 2.2, $P < 0.01$, for hospital admission, in multivariate analysis with adjustment for sex, age, comorbidities, socioeconomic factors; no correlation study of diabetes to race performed	Non-Hispanic African Americans had OR 2.7, $P = 0.007$, for hospital admission vs. non-Hispanic Whites, after adjustment for the same variables as listed for diabetes findings	Not examined
Raisi-Estabragh et al. (61)	U.K.	1,326 positive, 3,184 negative COVID-19 tests from UK Biobank	Diabetes not a risk for susceptibility to positive vs. negative COVID-19 test; no correlation study of diabetes to race performed	Hypertension, high cholesterol not risks for susceptibility to positive vs. negative COVID-19 test; Black, Asian, and minority ethnic group more susceptible to positive vs. negative COVID-19 test, with adjustment for age, sex, BMI, diabetes, hypertension, cholesterol, and socioeconomic factors	Not examined
El Chaar et al. (56)	NYC	4,260 deaths	Diabetes not investigated	Hispanic and Black patients had highest age-adjusted mortality rates per 100,000 (22.8% and 19.8%, respectively, vs. other ethnic groups) corresponding to the groups with the highest obesity rates, 25.7% and 35.4%, respectively, $P < 0.05$; the two NYC boroughs with highest mortality rates, Bronx (6%) and Brooklyn (5.4%), also had the highest obesity rates, 32% and 27%, respectively	Not examined

Continued on p. 2561

Table 3—Continued

Study	Location	Participants (*n*)	Diabetes findings	Comorbidities findings*	Select laboratory findings**
Millet et al. (62)	U.S.	Nationwide population demographics and COVID-19 deaths	Diabetes prevalence in counties with <13% Black residents was 11.1% vs. 13.9% in counties with ≥13% Black residents, *P* value not stated; diabetes prevalence did not correlate with counties by COVID-19 cases (rate ratio 0.97 [95% CI 0.92–1.03]) or deaths (rate ratio 1.01 [95% CI 0.88–1.16]), after adjustment for demographics, comorbidities, and socioeconomic factors	Counties with higher Black resident proportions (≥13%) had more COVID-19 cases (rate ratio 1.24, 95% CI 1.17–1.33) and deaths (rate ratio 1.18, 95% CI 1.00–1.40), after adjusting for county-level traits, e.g., age, comorbidities, poverty, and epidemic duration	Not examined

*Conditions comorbid with diabetes considered. **Select laboratory findings for significant differences reported in immune cell populations, cytokines, and biomarkers of infection and kidney, liver, and cardiac damage. Changes were reported if there were significant differences in either mean values or in the number of patients above a cutoff value.

proportion of Black residents (i.e., above national average, ≥13%) had more COVID-19 cases (rate ratio 1.24) and deaths (rate ratio 1.18), after adjustment for county-level traits, e.g., age, comorbidities, poverty, and pandemic duration. Diabetes prevalence was also higher (13.9% vs. 11.1%) in counties with high (≥13%) and low (<13%) proportion of Black residents but did not correlate with COVID-19 cases (rate ratio 0.97) or deaths (nonsignificant rate ratio 1.01), after adjustment for demographics, comorbidities, and socioeconomic factors. Thus, diabetes, or other cardiometabolic effects, may not be solely attributable to COVID-19 risk in Black patients. Finally, large population-based studies, OpenSAFELY and NHS England, found higher mortality risk for Asian and Black races, after adjustment for age, sex, comorbidities, and socioeconomic status (4,26,33).

Overall, Black, Hispanic, and possibly other races may be risk factors for serious COVID-19 infection or death, but the factors driving this disparity are presently unclear (Fig. 1).

COVID-19 and Diabetes Pathology: Collision and Collusion

Given the relatively short time that has elapsed since the SARS-CoV-2 pandemic broke out, its pathophysiology remains incompletely understood. However, like its predecessors SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 gains cellular entry by leveraging the ACE2 receptor, a master regulator of the renin-angiotensin system. The major viral spike glycoprotein (S1) binds to ACE2 (63), while proximal serine proteases, like the transmembrane serine protease 2, cleave the virus spike protein and ACE2, promoting viral internalization (64). Infection induces cell death, which triggers inflammatory cytokine production and inflammatory immune cell recruitment (65). SARS-CoV-2 also infects circulating immune cells, stimulating lymphocyte apoptosis and inflammatory cytokine secretion, known as "cytokine storm" (6). High circulating cytokine levels contribute to SARS-CoV-2–driven multiorgan failure and disrupted endocrine signaling and hyperglycemia surges (66). Widespread multitissue ACE2 expression, e.g., lung, heart, kidney, and nerve (67), leads to tropism, as validated by viral detection within multiple tissues (7,68). Tropism potentially constitutes another pathway to multiorgan damage in COVID-19 patients, e.g., acute cardiac injury (ACI) and acute kidney injury (AKI) (13,14).

Although the inflammatory, hyperglycemic, and tissue damage response is intensely acute in COVID-19 infection, it is mirrored by diabetes pathology (Fig. 2), which is characterized by chronic, low-grade inflammation, impaired glycemic control, and slowly progressive multitissue injury, e.g., diabetic microvascular (CKD, neuropathy, brain) and macrovascular (CVD) complications (8,69). Although the underlying reasons for the susceptibility of patients with diabetes to COVID-19 remain unclear, commonalities in pathology suggest that acute COVID-19–induced adverse reactions may superimpose on preexisting inflammation, glucose variability, and multitissue injury in patients with diabetes to aggravate outcomes (Fig. 1).

Do Preexisting Diabetes Complications Predispose Patients to Acute COVID-19–Induced Organ Damage?

Few studies have stratified COVID-19 patients by diabetes status to examine the possibility that preexisting micro- and macrovascular complications render patients susceptible to acute organ injury (Fig. 1). CORONADO ($n = 1,317$) demonstrated that preexisting microvascular (OR 2.14) and macrovascular (OR 2.54) complications independently associated with 7-day mortality (25), suggesting that the presence of diabetes complications may set patients on poorer clinical trajectories. In a NYC study of 5,449 severe COVID-19 patients, of whom 1,993 developed AKI, diabetes was a risk for renal damage, with 41.6% developing AKI vs. 28.0% who did not (70). Diabetes also correlated with progressive damage in AKI stage 1 (39.7%), stage 2 (43.2%), and stage 3 (43.5%) by Kidney Disease: Improving Global Outcomes (KDIGO) criteria. After adjustment for age, sex, and race, diabetes had an OR of 1.76 for AKI. However, the study did not state whether AKI correlated with preexisting CKD, since baseline CKD data were not available, although associations with preexisting CKD and AKI have been noted in meta-analysis (71).

Although diabetes was not an independent risk for COVID-19 death in a cohort of 153 patients with diabetes compared with age- and sex-matched individuals without diabetes, patients with diabetes were more likely to have preexisting CVD and be admitted to ICUs and experience acute complications (ACI, AKI, ARDS) (43). Nonsurvivor patients with diabetes had higher blood glucose levels and a greater chance of ACI or AKI, in addition to an altered inflammatory and immune system profile (see *Are Patients With Diabetes Predisposed to Acute COVID-19–Induced Inflammatory Response?*). Within a cohort with diabetes ($n = 952$), patients with well-controlled glucose were also less likely to suffer from hypertension and CVD. They were also at lowered risk of AKI (HR 0.12) and ACI (HR 0.24), after adjustment for comorbidities (3), indicating that even if preexisting microvascular complications contribute to acute organ injury, additional factors, such as glucose control or inflammation, may also participate.

Additional Aspects of COVID-19 Tropism Relevant to Diabetes

One particular aspect of COVID-19 tropism meriting close attention from a diabetes perspective is the possibility of increasing the incidence of β-islet damage–induced type 1 diabetes. Drawing parallels, SARS-CoV may have been responsible for acute type 1 diabetes onset by leveraging β-islet ACE2 expression to induce loss of islets (72). It is possible that COVID-19 might also trigger acute-onset type 1 diabetes in individuals predisposed to autoimmunity (73). Indeed, the multicenter regional data from North West London just reported an 80% increase in new-onset type 1 diabetes cases and diabetic ketoacidosis in children up to the age of 16 years during the COVID-19 pandemic peak (74). Moreover, COVID-19 tropism through ACE2 expression in adipose tissue may underlie the link to obesity as a serious infection risk, since adipose tissue could potentially serve as a reservoir of viral shedding (75).

Are Patients With Diabetes Predisposed to Acute COVID-19–Induced Inflammatory Response?

Although the full cytokine storm profile in COVID-19 is not fully characterized yet, hyperinflammation predicts serious disease (Fig. 1). Lymphopenia along with elevation in white blood cells (WBC), neutrophils, C-reactive protein (CRP), erythrocyte sedimentation (ESR), ferritin, IL-6, and procalcitonin (PCT) associates with poorer COVID-19 clinical course, defined as serious infection, ARDS, ICU admission, or death, in studies in multiple countries (Table 1). COVID-19 patients experience, in parallel to inflammation, elevated AST, brain natriuretic peptide, hypersensitive troponin I (hs-TnI), creatine kinase (muscle and brain type), lactate dehydrogenase (LDH), and creatinine (Cr), indicative of tissue damage. Clotting homeostasis is similarly compromised, e.g., with elevated D-dimer with longer thrombin or prothrombin time, which also correlate with clinical progression. A meta-analysis found higher AST (>40 units/L), Cr (≥133 μmol/L), D-dimer (>0.5 mg/L), hs-TnI (>28 pg/mL), LDH (>245 units/L), and PCT (>0.5 ng/mL) and lower WBC ($<4 \times 10^9$ per L) defines an OR >1 for critical illness (76).

Diabetes is also characterized by chronic, low-grade inflammation, which is also a prominent feature of its complications, diabetic CKD, CVD, and neuropathy (8,77,78). Several proinflammatory molecules from the COVID-19 cytokine storm cascade are shared with type 2 diabetes pathophysiology, such as CRP, IL-6 (77), and PCT (79). The underlying chronic inflammatory state in diabetes may be "locked and loaded" for virus-induced damage, promoting a vicious cycle of cytokine release and hyperglycemic surges, leading to more widespread multiorgan damage, including injury to tissues already weakened by preexisting diabetes complications.

Worryingly for patients with diabetes, and as an added layer of risk, they are more prone to cytokine storm, which predicts poorer outcomes (Table 1). Admission CRP (OR 1.93) and AST (OR 2.23) independently predicted 7-day mortality in the CORONADO COVID-19 patients with diabetes (25). In Chinese cohorts, patients with diabetes had a more inflammatory profile than patients without diabetes (3,27). More favorable inflammatory and tissue biomarker profiles were also evident in patients with type 2 diabetes with well-controlled versus poorly controlled blood glucose (3,30). Another study found differences in numerous inflammation and organ damage biomarkers in nonsurviving versus surviving patients with diabetes, which also correlated with glucose and HbA_{1c} levels (43). Moreover, elevated inflammation and organ damage biomarkers were present in COVID-19 patients with diabetes and hyperglycemia secondary versus without diabetes and with normoglycemia (34).

One inflammatory biomarker, with deep roots in diabetes pathophysiology, not widely investigated in COVID-19, is soluble urokinase-type plasminogen activator receptor (suPAR). In Greek ($n = 57$) and U.S. ($n = 21$) COVID-19 cohorts, we found that admission suPAR predicted severe respiratory failure (80). suPAR correlates

with diabetes risk (81) and reflects the underlying chronic inflammatory process of its micro- (82) and macrovascular complications (83).

The reasons for the susceptibility of patients with diabetes to COVID-19 are multifaceted and reflect the complex pathophysiology of both diabetes and COVID-19 infection. Diabetes and its comorbidities, inflammation, glucose variability, and other factors, may "collide and collude" to disproportionally set COVID-19 patients with diabetes on poorer clinical trajectories (Fig. 2).

Diabetes and COVID-19 Sequelae

It is becoming clear that COVID-19 survivors suffer from persistent symptoms (84) and may also face a lifetime of sequelae, which draws parallels to SARS-CoV and MERS-CoV (10,85). Although the pandemic has not yet lasted long enough to measure long-term outcomes, the evidence to date suggests a significant burden of possibly irreversible new complications. For instance, COVID-19, like SARS-CoV and MERS-CoV, may aggravate preexisting CVD or even induce new cardiac pathology (86), including in patients with type 2 diabetes (87). COVID-19 patients with preexisting CKD are likelier to suffer AKI (71). COVID-19 also elicits neurological manifestations (88) and cognitive impairment (89), which exhibit shared pathology with diabetes through cytokine storm, hypercoagulability, and endothelial dysfunction. Since patients with diabetes have a high burden of preexisting comorbidities that share pathology with COVID-19–induced damage, it is possible that COVID-19 survivors with diabetes may be particularly at risk for long-term sequelae, although this remains to be determined (Fig. 1). Moreover, the COVID-19 pandemic has seen significant racial health disparities (57). Indeed, SARS-CoV outbreak survivors have reported psychological and financial hardship, even years later (10,90). Thus, COVID-19 could possibly amplify socioeconomic disparities.

Conclusions: A Collision and Collusion of Two Diseases

COVID-19 has collided with diabetes, creating especially susceptible populations of patients with both COVID-19 and diabetes. Vulnerabilities may be further amplified by comorbid medical conditions, racial and ethnic disparities, and access to medical care. Thus, in addition to parallels in pathology, the two diseases also reflect their distinct and shared scope of socioeconomic burdens. As our understanding of COVID-19 increases through the lens of diabetes, identifying prognostic factors could help stratify individuals with diabetes most at risk. Moreover, as more evidence comes to light, improvements in short- and long-term care for patients with and without diabetes will develop while we all await a vaccine.

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