COVID-19 in people with diabetes: understanding the reasons for worse outcomes

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Since the initial COVID-19 outbreak in China, much attention has focused on people with diabetes because of poor prognosis in those with the infection. Initial reports were mainly on people with type 2 diabetes, although recent surveys have shown that individuals with type 1 diabetes are also at risk of severe COVID-19. The reason for worse prognosis in people with diabetes is likely to be multifactorial, thus reflecting the syndromic nature of diabetes. Age, sex, ethnicity, comorbidities such as hypertension and cardiovascular disease, obesity, and a pro-inflammatory and pro-coagulative state all probably contribute to the risk of worse outcomes. Glucose-lowering agents and anti-viral treatments can modulate the risk, but limitations to their use and potential interactions with COVID-19 treatments should be carefully assessed. Finally, severe acute respiratory syndrome coronavirus 2 infection itself might represent a worsening factor for people with diabetes, as it can precipitate acute metabolic complications through direct negative effects on β-cell function. These effects on β-cell function might also cause diabetic ketoacidosis in individuals with diabetes, hyperglycaemia at hospital admission in individuals with unknown history of diabetes, and potentially new-onset diabetes.

Introduction

In December, 2019, a cluster of cases of atypical interstitial pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China. Following the rapid spread of COVID-19, WHO on March 11, 2020, declared COVID-19 a global pandemic. As a result, social containment measures have been adopted worldwide and health-care systems reorganised to cope with a growing number of acutely ill patients. At the time this Review was written, more than 12 million cases and more than 550 000 deaths have been reported worldwide.[1] Among those with severe COVID-19 and those who died, there is a high prevalence of concomitant conditions including diabetes, cardiovascular disease, hypertension, obesity, and chronic obstructive pulmonary disease.[2] The fatality rate is particularly high in older patients, in whom comorbidities are common.[2]

Most of the available information refers to patients with type 2 diabetes,[3,4] and in this Review we mainly refer to patients with type 2 diabetes, unless otherwise stated. In previous disease epidemics, a greater risk of viral infection was observed in people with diabetes.[5] This does not seem to be the case for COVID-19,[1] though diabetes is more common among those with severe COVID-19. Data from two hospitals in Wuhan including 1561 patients with COVID-19 showed that those with diabetes (9·8%) were more likely to require admission to an intensive care unit (ICU) or to die.[6] Similarly, in a British cohort of 5693 patients with COVID-19 in hospital, the risk of death was more common in those with uncontrolled diabetes (hazard ratio [HR] 2·36, 95% CI 2·18–2·56).[7] Whether such worse prognosis is due to diabetes per se or to concomitant morbidities and risk factors remains to be fully elucidated. This Review is, therefore, intended to provide a systematic assessment of potential prognostic factors in patients with diabetes with COVID-19.

Epidemiology

Diabetes is known to confer increased risk for infections. Previous studies have shown a J-curve relationship between HbA_{1c} and risk of being admitted to hospital for infections in general, and infections of the respiratory tract in particular. An increased risk of infection was reported during previous outbreaks of severe acute respiratory syndrome,[5] Middle East respiratory syndrome,[8] and H1N1 influenza virus;[9] however, this doesn't seem to be the case for COVID-19. In an analysis, the prevalence of diabetes in 1590 Chinese patients with COVID-19 was 8·2%, similar to the prevalence of diabetes in China. However, the prevalence of diabetes rose to 34·6% in patients with severe COVID-19.[10] In a meta-analysis of six Chinese studies, the prevalence of diabetes was 9·7% in the whole COVID-19 cohort (n=1527), similar to the estimated diabetes prevalence in China (10·9%).[11] In 146 patients with a mean age of 65·3 years admitted to hospital for COVID-19 in northern Italy, a prevalence of diabetes of 8·9% was reported, slightly lower than the diabetes prevalence in the same region for the same age stratum (11%).[12]

Diabetes does not seem to increase the risk of COVID-19 occurring, although diabetes is more frequent in patients with severe COVID-19 (table 1). In a Chinese retrospective study, patients with diabetes had more severe pneumonia, higher concentrations of lactate dehydrogenase, α-hydroxybutyrate dehydrogenase, alanine aminotransferase, and γ-glutamyl transferase, and fewer lymphocytes with a higher neutrophil count. In the same study, a subgroup of 24 patients with diabetes had greater mortality compared to 26 patients without diabetes (16·5% *vs* 0%).[21] In a prospective cohort study of patients with COVID-19 from New York City (NY, USA), the prevalence of diabetes and obesity was higher in individuals admitted to hospital than those not admitted to hospital (34·7% *vs* 9·7% for diabetes and 39·5% *vs* 30·8% for obesity, respectively).[13] In a meta-analysis of

eight studies,[14] patients with COVID-19 with diabetes had an increased risk of ICU admission. In a retrospective study[13] of 191 patients with COVID-19 admitted to hospital, compared with survivors (n=137) those who died (n=54) had a higher prevalence of hypertension (23% *vs* 48%), diabetes (14% *vs* 31%), and coronary heart disease (1% *vs* 24%). In Italy, an analysis[22] of 27 955 patients who died from COVID-19 showed a prevalence of diabetes of 31·1%.

A survey done in England (UK)[20] showed that of 23 804 patients with COVID-19 dying in hospital, 32% had type 2 diabetes and 1·5% had type 1 diabetes, with 2·03 and 3·5 times the odds of dying compared with patients without diabetes, respectively. In the French population of the CORONADO study,[23] 3% had type 1 diabetes, 88·5% had type 2 diabetes, 5·4% had other type diabetes, and 3·1% were diagnosed at admission. A further study[24] showed adjusted HRs with HbA_{1c} greater than 86 mmol/mol (10%) compared with HbA_{1c} 48–53 mmol/mol (6·5%–7·0%) of 2·19 (95% CI 1·46–3·29) for type 1 diabetes and 1·62 (95% CI 1·48–1·79) for type 2 diabetes.

In summary, patients with COVID-19 with diabetes have a worse prognosis, most probably because of the concurring effect of multiple factors. In an American survey,[25] 33 individuals with type 1 diabetes with COVID-19 were identified; they were young (mean age 24·8 years [SD 17·49]), with high glucose concentrations at presentation and diabetic ketoacidosis reported in 45·5% of the cases. Similar to those with type 2 diabetes, obesity, hypertension, and cardiovascular disease were the most common comorbidities.

	Article type	Study population	Prevalence of diabetes	Outcome	Risk
Zhang et al[3]	Retrospective	258	24%	Mortality	3·64 (1·08–12·21)*
Kumar et al[4]	Meta-analysis	16 003	9·8%	Severe disease	2·75 (2·09–3·62)*
Kumar et al[4]	Meta-analysis	16 003	9·8%	Mortality	1·90 (1·37–2·64)*
Guan et al[10]	Retrospective	1590	NA	Composite†	1·59 (1·03–2·45)‡
Li et al[11]	Meta-analysis	1525	9·7%	ICU admission§	2·21 (0·88–5·57)¶
Fadini et al[12]	Meta-analysis	1687	NA	Severe disease	2·26 (0·98–4·82)‖
Fadini et al[12]	Meta-analysis	355	35·5%	Mortality	1·75‖
Petrilli et al[13]	Retrospective	5279	22·6%	Hospital admission	2·24 (1·84–2·73)*
Roncon et al[14]	Meta-analysis	1382	NA	ICU admission	2·79 (1·85–4·22)*
Roncon et al[14]	Meta-analysis	471	NA	Mortality	3·21 (1·82–5·64)*
Zhou et al[15]	Retrospective	191	19%	Mortality	2·85 (1·35–6·05)*
Zhu et al[16]	Retrospective	7337	13%	Mortality	1·49 (1·13–1·96)‡
Yan et al[17]	Retrospective	193	25%	Mortality	1·53 (1·02–2·3)‡
Sardu et al[18]	Retrospective	59	44%	Survival	0·172 (0·051–0·576)‡
Yang et al[19]	Meta-analysis	4648	NA	Severe disease	2·07 (0·88–4·82)*
Barron et al[20]	Cohort study	61 414 470	0·4% type 1 diabetes	Mortality	3·50 (3·15–3·89)*
Barron et al[20]	Cohort study	61 414 470	4·7% type 2 diabetes	Mortality	2·03 (1·97–2·09)*

ICU=intensive care unit. NA=not given. *Odds ratio (95% CI). †ICU admission, or invasive ventilation, or death. ‡Hazard ratio (95% CI). §Calculated for 1056 patients (in three of six studies). ¶Risk ratio (95% CI). ‖Rate ratio (95% CI not given).

Table 1: **COVID-19 outcomes according to pre-existing diabetes**

Potential prognostic factors

Age, sex, and ethnicity

Older age and male sex are epidemiological features related to a higher prevalence of COVID-19 and a more severe clinical course. In the early phase of the outbreak, the highest prevalence of COVID-19 occurred in older people in most of the regions of the world, with the exception of South Korea[26] where the highest rate of confirmed SARS-CoV-2 infection occurred in those aged 20–29 years. However, an increased prevalence in those below the age of 30 years has been recently observed in Florida (USA), most probably due to social reasons. In all other countries the highest prevalence of COVID-19 has been in older people. In a large case series of the Chinese pandemic (72 314 cases, updated to Feb 11, 2020),[27] the peak of morbidity was in people aged 50–59 years. The overall case-fatality rate was 2·3% but this increased up to 14·8% in individuals aged 80 years and older.

The prevalence of diabetes increases with age in both the general population and in patients with COVID-19. Accordingly, the average age of patients with COVID-19 with diabetes is older than those without diabetes. In one survey,[28] patients with diabetes were at least 10 years older than patients without diabetes. Moreover, age was associated with a greater odds ratio (OR) of in-hospital death that was similar in individuals without diabetes (multivariate OR 1·09, 95% CI 1·07–1·12) and those with diabetes (1·09, 1·04–1·15). A separate study[6] of a matched population of patients with COVID-19 with and without diabetes reported that survivors were younger than non-survivors, with age 70 years and older being an independent predictor of in-hospital death (no diabetes HR 5·87, 95% CI 1·88–18·33; diabetes HR 2·39, 1·03–5·56).

Despite overall similar sex distribution of people infected with SARS-CoV-2, (male 51%, female 49%), the case-fatality rate has been higher in males (2·8%) than in females (1·7%).[19] A study[7] confirmed age and male sex as risk factors for worse outcomes in COVID-19, with those aged 80 years and older having a 12-times higher risk compared with those aged 50–59 years and males having twice the risk as females (HR 1·99, 95% CI 1·88–2·10).

Non-white ethnic groups seem to be at greater risk as indicated by HRs adjusted for age and sex ranging between 1·83 and 2·17 for black, Asian or Asian British, and mixed ethnicities compared with white people.[7] This finding confirms a US report on a link between racial minorities and worse outcomes from COVID-19. An analysis[29] of a database representative of 10% of the US population showed that 33% of people admitted to hospital with COVID-19 were African Americans, even though they represent 18% of the sample population. The Johns Hopkins University and American Community Survey[30]

reported that in 131 predominantly black counties in the USA, infection and death rates were more than three times and six times higher, respectively, than in predominantly white counties. In New York City, Hispanic or Latin people account for 28% of the population, but 34% of COVID-19 deaths.[29] In New Mexico, Native Americans represent 11% of the population, but 37% of COVID-19 cases.[29]

The higher incidence and worse outcomes of COVID-19 reported in ethnic minority groups are unlikely to reflect biological factors, and are predominantly due to lifestyle and socioeconomic factors. Although data fully adjusted for comorbidities are not yet available, a higher prevalence of cardiovascular risk factors such as hypertension, diabetes, and obesity in ethnic minorities compared with the white population might partly account for the increased risk of poor outcome in these minority populations. These populations are also more likely to be socioeconomically disadvantaged as they more often live in poor and overcrowded houses and are employed in jobs requiring human interaction with resulting increased exposure to the risk of virus transmission. However, in India, Pakistan, and Bangladesh, despite a high prevalence of diabetes and deprivation, a relatively low COVID-19 mortality has been reported so far.[31] This finding has suggested a potential geographical or climatic effect on the spreading of the infection. However, a careful geopolitical analysis[32] considering latitude, temperature, and humidity could only find a weak negative association with relative humidity.

In summary, available data suggest that age is associated with worse outcomes in COVID-19, and it can be hypothesised that this relationship is stronger in people with diabetes for at least three reasons. First, the prevalence of diabetes increases with age to reach a peak in people older than 65 years. Second, people older than 65 years are more likely to have a longer duration of diabetes and a greater prevalence of diabetic complications. Third, diabetes and older age often correlate with comorbidities such as cardiovascular disease, hypertension, and obesity.

Comorbidities

In a retrospective analysis of patients with COVID-19,[6] those with diabetes had a greater prevalence of hypertension (56·9%), cardiovascular disease (20·9%), and cerebrovascular disease (7·8%) than those without diabetes (28·8%, 11·1%, and 1·3%, respectively). Moreover, in the patients with diabetes, non-survivors had a greater prevalence of comorbidities than survivors (hypertension 83·9% *vs* 50·0%; cardiovascular disease 45·2% *vs* 14·8%; cerebrovascular disease 16·1% *vs* 5·7%; chronic pulmonary disease 12·9% *vs* 3·3%; and chronic kidney disease 6·5% *vs* 3·3%). In a Cox multi-regression analysis,[6] in patients with diabetes but not in those without diabetes, hypertension (HR 3·10, 95% CI 1·14–8·44), cardiovascular disease (1·87, 0·88–4·00), and chronic pulmonary disease (2·77, 0·90–8·54) were independent risk factors for in-hospital death. These findings were also noted in 136 patients with diabetes of 904 patients with COVID-19.[28] In the patients with COVID-19, those with diabetes more commonly had hypertension, cardiovascular disease, nervous system disease, and chronic kidney disease; cardiovascular disease, nervous system disease, and chronic kidney disease were all associated with risk for in-hospital death and poor prognosis. In the CORONADO study,[23] an estimated glomerular filtration rate on admission to hospital of 60 mL/min per 1·73 m² or less was an independent predictor of early death in patients with diabetes. SARS-CoV-2 might directly target the kidney through an angiotensin-converting enzyme (ACE) 2-dependent pathway, causing acute renal impairment and increased lethality.[33]

Hypertension

Arterial hypertension is by far the most frequent comorbidity seen in patients with COVID-19.[34] It has been speculated that the high prevalence of the infection could be due to use of ACE inhibitors since SARS-CoV-2 binds to ACE2 to enter target cells.[35] ACE2 is expressed in the lung, heart, liver, kidney, ileum, and brain and is physiologically involved in anti-inflammatory responses.[36] Experimental evidence[37,38] suggests that ACE inhibitors and angiotensin receptor blockers increase the expression of ACE2, and it was proposed that these drugs could facilitate target organ infection and promote progression of the disease. However, this evidence was obtained in in vitro and animal studies. Given its structural differences with ACE, ACE2 does not represent a target of these drugs.[37] Moreover, the interaction between ACE inhibitors and the renin–angiotensin system is complex and not completely understood in humans.[39] SARS-CoV-2 has been claimed to increase the expression of angiotensin II with subsequent downregulation of ACE2 and loss of anti-inflammatory effect in the respiratory tract, resulting in alveolar wall thickening, oedema, inflammatory infiltration, and bleeding. Moreover, a favourable effect of ACE inhibitors and angiotensin receptor blockers on the risk of community acquired pneumonia, especially in Asian populations, has been suggested.[40] Initial reports[14] on 8910 patients with COVID-19 from 11 countries could not detect an association between ACE inhibitors or angiotensin receptor blockers and the risk of in-hospital death. A population-based case-control study[41] from Lombardy, an Italian region particularly affected by the pandemic, led to similar conclusions. A Chinese study has even shown a lower rate of severe diseases and a trend toward a lower inflammatory response in 17 patients with COVID-19 treated with ACE inhibitors or angiotensin receptor blockers versus 25 patients given other anti-hypertensive drugs.[42] In summary, ACE inhibitors are unlikely to account for the association between COVID-19 and hypertension.[43]

Cardiovascular disease

Patients with COVID-19 have a high prevalence of cardiovascular disease.[11] Cases of acute myocarditis associated with COVID-19 have been reported[44] and a direct myocardial injury has been postulated. The evidence for myocardial injury is largely indirect, with no evidence of viral genomes from myocardial biopsy samples.[45] In an autopsy report[46] for 23 patients with COVID-19, 13 showed cardiac manifestations, along with pulmonary involvement. Three patients had obesity and had multifocal acute cardiomyocyte injury without inflammatory cellular infiltrates, lymphocytic myocarditis, or lymphocytic pericarditis associated with signs of chronic cardiac disease. In a meta-analysis[47] of 4189 patients from 28 observational studies, patients with more severe COVID-19 had higher troponin concentrations, which was associated with an increased risk of death.

A manifestation of secondary cardiac involvement in COVID-19 is stress-induced (Takotsubo) cardiomyopathy.[45] Cardiovascular complications might also develop because of reduced systemic oxygenation due to pneumonia and concomitant increased cardiac demand, by immune dysregulation, electrolyte imbalance, or because of adverse effects of drugs such as hydroxychloroquine and azithromycin.[48]

Obesity

Many reports have linked obesity to more severe COVID-19 illness and death.[6,23,49] Several mechanisms can account for this association. The first concerns the detrimental restrictive ventilatory effect of abdominal fat.[50] In a French study,[51] the risk for invasive mechanical ventilation in patients with COVID-19 admitted to an ICU was more than seven times higher in those with a BMI of more than 35 kg/m² than those with a BMI of less than 25 kg/m². Second, in addition to the ventilatory defect, the respiratory dysfunction in patients with severe COVID-19 might depend on impaired lung perfusion due to intravascular disseminated coagulation.[52] In line with this hypothesis, low-molecular-weight heparin was found to reduce mortality.[53] Obesity and diabetes are prothrombotic conditions that might contribute to worse prognosis in patients with COVID-19. In an autopsy study from Germany,[54] deep venous thrombosis was found in seven of 12 patients (58%) and pulmonary embolism was the direct cause of death in four. Of these patients, the BMI of those who died from pulmonary embolism was 36·8 kg/m². Finally, obesity is associated with immune dysregulation and chronic inflammation that could mediate progression toward organ failure in severe COVID-19 patients.

Myocarditis and cardiomyocyte dysfunction could be worsened by local biological effects of epicardial adipose tissue,[55] a source of adipokines and pro-inflammatory mediators, and the volume of epicardial adipose tissue is directly associated with BMI.[56] Moreover, ACE2 is highly expressed in the epicardial adipose tissue of patients with obesity. This could promote virus internalisation into the adipocytes and enhance tumour necrosis factor (TNF) α and IL-6 release. Liver steatosis might also play a role. A Chinese study[57] reported a six-times increased risk of severe COVID-19 in patients with a BMI of more than 25 kg/m² and metabolic associated fatty liver disease compared with patients without obesity. Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis are common in people with abdominal obesity and diabetes.[58] Elevated aspartate aminotransferase concentrations have been associated with poorer prognosis in patients with COVID-19.[23,59] The extent to which SARS-CoV-2 could directly affect liver function remains to be established as ACE2 is mainly expressed in cholangiocytes.[60]

Obesity and diabetes are characterised by chronic low-grade inflammation with increased concentrations of pro-inflammatory leptin and reduced anti-inflammatory adiponectin. Additionally, people with obesity are often physically inactive, more insulin resistant, and with gut dysbiosis, which might increase the inflammatory response to infection with SARS-CoV-2. Moreover, individuals with obesity have lower vitamin D concentrations,[61] which could also reduce the immune response. The role of vitamin D supplementation is currently being investigated in ongoing clinical trials.

Inflammation

SARS-CoV-2 infects not only cells of the upper respiratory system and alveolar epithelial cells in the lung but also, among others, circulating immune cells (CD3, CD4, and CD8 T cells) inducing apoptosis of lymphocytes to an extent that reflects the severity of SARS-CoV-2 infection.[62] As T cells of the adaptive immune system inhibit overactivation of innate immunity,[63] the resulting lymphocytopenia might suppress the innate immune system and enhance secretion of cytokines.[64] The over-production of pro-inflammatory cytokines (TNFα, IL-6, IL-1β, and CXC-chemokine ligand 10) results in a so-called cytokine storm, which leads to high risk of vascular hyperpermeability, multiorgan failure, and death.[65]

High blood concentrations of inflammatory markers (ie, C-reactive protein, procalcitonin, and ferritin), a high neutrophil-to-lymphocyte ratio, and increased blood concentrations of inflammatory cytokines and chemokines have been associated with both COVID-19 severity and death.[13,15,66] Post-mortem analyses of patients with COVID-19[67–69] have revealed inflammatory infiltration of the lungs, heart, spleen, lymph nodes, and kidneys. In those with severe COVID-19, a study[70] found higher concentrations of leukocytes (5·3 *vs* 4·5×10⁹ L, p=0·014), C-reactive protein (47·6 *vs* 28·7 mg/L, p<0·001), and procalcitonin (0·1 *vs* 0·05 ng/mL, p<0·001), and lower lymphocyte percentages (median 0·7% [IQR 0·5–1·0] *vs* 0·8% [0·6–1·2], p=0·048) compared with patients with non-severe COVID-19. Moreover, C-reactive protein concentrations of more than 200 mg/L and ferritin

concentrations of more than 2500 ng/mL at hospital admission are risk factors for critical COVID-19.[13] Several reports confirmed these results[71,72] and a meta-analysis[66] including more than 3000 patients with COVID-19 identified high concentrations of IL-6, IL-10, and serum ferritin as strong indicators for severe disease. A dysregulated inflammatory innate and adaptive impaired immune response might occur in patients with diabetes, accounting for the systemic tissue damage and respiratory and multiorgan failure. The cytokine storm is more likely to develop in patients with diabetes, as diabetes is already characterised by low-grade chronic inflammation. Moreover, in the case of high viral load, the capacity to raise an acute immune response might be compromised in patients with diabetes, exposing them to more severe adverse effects. One study[21] reported that patients with COVID-19 with diabetes had higher concentrations of inflammation-related biomarkers, such as C-reactive protein, serum ferritin, and IL-6, and a higher erythrocyte sedimentation rate, compared with patients with COVID-19 without diabetes. These results were supported by findings from a multicentre study[16] in a Chinese population of patients with COVID-19 (952 with diabetes and 6385 without diabetes), showing that those with diabetes had a higher incidence of lymphopenia (44·5% *vs* 32·6%), and elevated inflammatory biomarkers (C-reactive protein 57·0% *vs* 42·4% and procalcitonin 33·3% *vs* 20·3%]. For patients with COVID-19, those with diabetes are more susceptible to the destructive effect of the cytokine storm than those without diabetes.

Coagulation

COVID-19 has been found to be associated with increased coagulation activity.[73] The endothelial dysfunction associated with hypoxia can favour intra-vessel coagulation during COVID-19 infection. Post-mortem studies have found changes in lung vessels, massive pulmonary interstitial fibrosis, variable degrees of haemorrhagic pulmonary infarction, severe endothelial injury, widespread vascular thrombosis with nearly total occlusion of alveolar capillaries, structurally deformed capillaries, and growth of new vessels through a mechanism of intussusceptive angiogenesis.[46,74] Moreover, intravascular disseminated coagulation can be the terminal event in severe COVID-19,[75] and anticoagulant therapy seems to improve prognosis.[53]

Diabetes is associated with a prothrombotic state, with an imbalance between clotting factors and fibrinolysis and an increased risk of thromboembolic events.[76] In a retrospective Chinese study[17] in patients with diabetes admitted to hospital for COVID-19, non-survivors had longer prothrombin times and higher concentrations of D-dimer. Patients with COVID-19 with diabetes often present other risk factors such as obesity, older age, and being admitted to hospital that could increase the pro-coagulative state and the risk of thrombotic complications.

Hyperglycaemia

Despite its syndromic nature, diabetes is still identified as a disturbance of glucose homoeostasis and progressive worsening of hyperglycaemia. In previous infectious disease epidemics, a high glucose concentration was shown to be an independent predictor of death and morbidity. This is likely to also be the case for COVID-19.[11,77] The role of hyperglycaemia, however, requires a systematic analysis, as suggested by Scheen and colleagues,[78] as the role of glycaemic control before hospital admission, at the time of hospital admission, and during treatment in hospital needs to be considered.

Glycaemic control before hospital admission

A cohort analysis[5] of more than 5500 patients with COVID-19 in the UK found that poor glycaemic control before hospital admission, as indicated by HbA_{1c} concentrations, was associated with a high risk of in-hospital death. In a model adjusted for sociodemographic variables and comorbidities, the HR for in-hospital death was greater in patients with HbA_{1c} of 58 mmol/mol (7·5%) or more (3·36, 95% CI 2·18–2·56) than in those with lower HbA_{1c} (1·50, 1·40–1·60) or those without recent HbA_{1c} measurement (1·87, 1·63–2·16).[7] Findings from a separate study[24] also suggested a higher risk of mortality from COVID-19 in patients with either type 1 or type 2 diabetes with HbA_{1c} of more than 86 mmol/mol (10%) compared with those with HbA_{1c} of less than 48 mmol/mol (6·5%). Surprisingly, in the CORONADO study[23] no association was noted between HbA_{1c} concentrations and the primary composite outcome (death and tracheal intubation for mechanical ventilation within the first 7 days after hospital admission) in patients with diabetes admitted to hospital with COVID-19. However, the mean HbA_{1c} value (65 mmol/mol [8·1%]) at admission in this study was higher than the average HbA_{1c} values (54 mmol/mol [7·1%]) in the age-matched French population in a separate study.[79]

Plasma glucose at admission

Despite no association being found between HbA_{1c} and outcomes in the CORONADO study, an association was noted between plasma glucose concentration at admission and the primary outcome. In a retrospective study[80] of 85 patients with COVID-19, hyperglycaemia at hospital admission was the best predictor of worst chest radiographic imaging results. Another study[81] found a higher risk of a composite outcome (ICU admission, mechanical ventilation, and death) in patients with hyperglycaemia at admission (fasting blood glucose >7 mmol/L) and without history of diabetes compared with patients without diabetes and normoglycaemia (OR 5·47, 95% CI 1·56–19·82). This finding is supported by results from a retrospective analysis[82] that showed death occurred in 40 of 96 uncontrolled patients with hyperglycaemia (41·7%) compared with deaths in 13 of 88 patients with diabetes (14·8%, p<0·001). Altogether,

these results highlight the need for improving glycaemic control in all patients presenting with hyperglycaemia, irrespective of a known diagnosis of diabetes.

In-hospital glycaemic control

Random hyperglycaemia during treatment in hospital was noted to contribute to worse prognosis for patients with COVID-19 in Wuhan.[83] In 1122 patients with COVID-19 admitted to hospital in the USA,[84] the mortality rate was four times higher in those with diabetes or hyperglycaemia during the hospital stay (28·8%) than those with normoglycaemia (6·2%). Moreover, mortality was higher in those with hyperglycaemia and without known diabetes than in patients with known diabetes.[84] Another study[77] showed that hyperglycaemia during treatment in hospital was a risk factor for death in patients with severe COVID-19 (adjusted HR 1·8, 95% CI 1·1–2·8). Patients with COVID-19 with diabetes[16] with an in-hospital median blood glucose concentration of less than 6·4 mmol/L (IQR 5·2–7·5) had lower incidences of lymphopenia (30·5% *vs* 49·6%), neutrophilia (10·7% *vs* 19·4%), increases in C-reactive protein (47·5% *vs* 59·5%), and procalcitonin (24·2% *vs* 35·0%) than patients with a median blood glucose concentration of 7·5 mmol/L or higher. Good glycaemic control was also associated with a lower rate of complications and all-cause mortality.[16] These results were confirmed in a propensity-matched score analysis, matching diabetes-related comorbidities.[16]

An unusually high number of COVID-19 patients developing diabetic ketoacidosis or hyperglycaemic hyperosmolar syndrome have been noted[85] and negative outcomes during COVID-19 have been reported in two clinical cases of diabetic ketoacidosis and hyperglycaemic hyperosmolar syndrome.[86] In one analysis,[87] ketosis occurred in 6·4% of patients with COVID-19 and its prevalence rose to 11·6% in patients with COVID-19 with diabetes, resulting in a high mortality rate (33·3%). In the CORONADO study,[23] 11·1% of the participants had diabetes-related disorders at admission including 132 patients with severe hyperglycaemia and 40 with ketosis, of whom 19 had diabetic ketoacidosis. Although ketosis might have resulted from discontinuation of glucose-lowering drugs because of anorexia before hospital admission, a direct effect of SARS-CoV-2 should be considered. The virus binds to ACE2 receptors, which, among other locations, are expressed in pancreatic tissue and β-cells in particular.[36] Therefore, an acute loss of insulin secretory capacity along with a stress condition and the cytokine storm could lead to a rapid metabolic deterioration with development of diabetic ketoacidosis or hyperglycaemic hyperosmolar syndrome. Additionally, hyperglycaemic hyperosmolar syndrome is likely to increase the risk of thrombosis that already characterises severe COVID-19. Because of the severity of diabetic ketoacidosis in patients with COVID-19, ad hoc recommendations for its treatment have been released in the UK.[85]

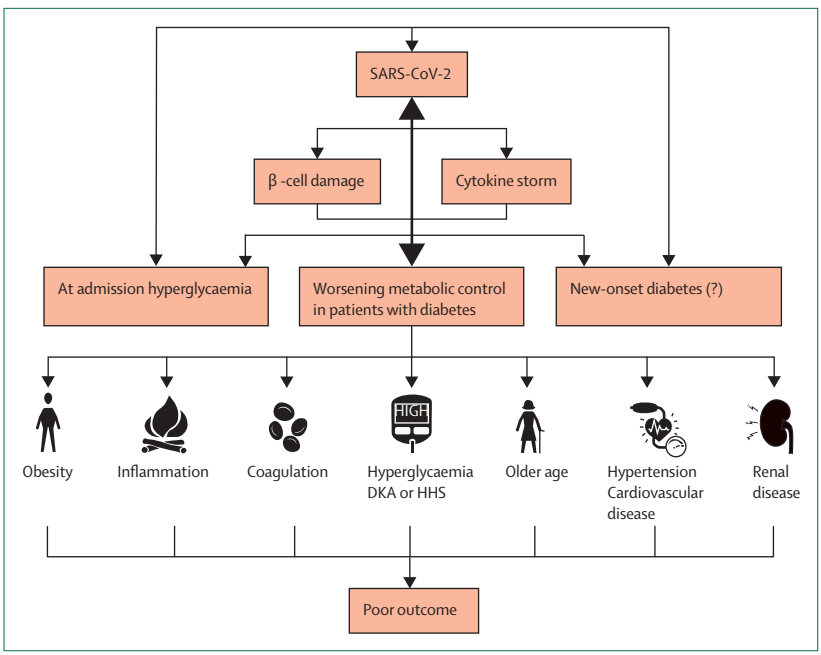

Figure: **Synopsis of the reciprocal effects of diabetes and COVID-19**
The relationship between diabetes and COVID-19 is biunivocal. On one hand, people with diabetes have worse outcomes because of multiple associated conditions enhancing the risk. On the other hand, SARS-CoV-2, because of its tropism for the β-cell, might cause new-onset diabetes or sustain hyperglycaemia at hospital admission. The impairment of β-cell function along with the inflammatory cytokine storm and counter-regulatory hormonal responses can precipitate further acute metabolic complications (DKA or HHS). New-onset diabetes, hyperglycaemia at admission, and acute metabolic deterioration, in turn, can further worsen COVID-19 outcomes. DKA=diabetic ketoacidosis. HHS=hyperglycaemic hyperosmolar syndrome.

The SARS-Cov-2 tropism for the β-cell could cause acute impairment of insulin secretion or destruction of β-cells resulting in de novo development of diabetes. This hypothesis is supported by a previous observation[88] that infection with human herpesvirus 8 in a sub-Saharan African population induced ketosis-prone type 2 diabetes. In line with this view, new-onset diabetes has been reported in patients with COVID-19 being treated in hospital.[82,89] In a population of 453 patients with COVID-19,[82] 94 were identified with new-onset diabetes (defined as first recognition of fasting plasma glucose ≥7 mmol/L and HbA_{1c} ≥48 mmol/mol (6·5%) at hospital admission); additionally, these individuals had a greater risk of mortality (HR 9·42, 95% CI 2·18 0–40·7) than those with hyperglycaemia (3·29, 0·65–16·6) or diabetes (4·63, 1·02–21·0).

In summary, poor glycaemic control at hospital admission and during the hospital stay worsens outcomes for patients with COVID-19. Moreover, consideration should be given for a direct effect of SARS-CoV-2 on β-cell function and survival, causing worsening rapid and severe deterioration of metabolic control in people with pre-existing diabetes or leading to the development of new-onset diabetes (figure). In people with hyperglycaemia, glycaemic control should be ensured to reduce the risk of threatening metabolic complications (table 2), which should integrate all therapeutic

	Article type	Study population	Prevalence of diabetes	Parameter	Outcome	Risk
Williamson et al[7]	Cohort study	17 425 445*	10%	HbA_{1c} ≥58 mmol/mol (7·5%)	Mortality	2·36 (2·18–2·56)†
Holman et al[24]	Cohort study	265 090‡	100% type 1 diabetes	HbA_{1c} >86 mmol/mol (10%)	Mortality	2·19 (1·46–3·29)†
Holman et al[24]	Cohort study	2 889 210‡	100% type 2 diabetes	HbA_{1c} >86 mmol/mol (10%)	Mortality	1·62 (1·48–1·79)†
Sardu et al[18]	Retrospective	59	44%	Admission glycaemia >7·7 mmol/L	Survival	0·285 (0·084–0·964)†
Li et al [76]	Retrospective	269	19%	Hyperglycaemia	Mortality	1·77 (1·11–2·84)†
Zhu et al[16]	Retrospective	818	100%	Median glycaemia during hospital stay 6·4 mmol/L (IQR 5·2–7·5)	Mortality	0·13 (0·04–0·44)†
Zhu et al[16]	Retrospective	818	100%	Median glycaemia during hospital stay 6·4 mmol/L (IQR 5·2–7·5)	ARDS	0·41 (0·25–0·66)†
Zhu et al[16]	Retrospective	818	100%	Median glycaemia during hospital stay 6·4 mmol/L (IQR 5·2–7·5)	Heart injury	0·21 (0·07–0·59)†
Zhu et al[16]	Retrospective	818	100%	Median glycaemia during hospital stay 6·4 mmol/L (IQR 5·2–7·5)	Kidney injury	0·22 (0·05–1·03)†
Chen et al[28]	Retrospective	904	15%	Hyperglycaemia	Mortality	1·08 (1·01–1·16)§

ARDS=acute respiratory distress syndrome. *General practice records managed by The Phoenix Partnership. †Adjusted hazard ratio. ‡Individuals registered with a general practice in England, UK. §Adjusted odds ratio.

Table 2: **COVID-19 outcomes according to glycaemic control**

manoeuvres put in place to reduce the risk of severe outcomes and mortality. Finally, achievement and maintenance of glycaemic control should take into consideration the implications of the use of different glucose-lowering agents in the setting of COVID-19.

Glucose-lowering agents

Use of glucose-lowering agents might raise specific considerations in patients with COVID-19 (table 3). In the presence of mild COVID-19 in an out-patient setting, usual glucose-lowering therapies for patients with diabetes could be continued if the patient eats and drinks adequately and a more frequent blood glucose-monitoring regimen is implemented.[90] Patients admitted to hospital for severe COVID-19 might need modifications to their diabetes therapy, including withdrawing ongoing treatments and initiating insulin therapy. Such a decision should be based on the severity of COVID-19, nutritional status, actual glycaemic control, risk of hypoglycaemia, renal function, and drug interactions. Although insulin treatment has been recommended in patients with diabetes with severe COVID-19,[90] one study[28] showed worse clinical outcomes and a worse laboratory results profile in patients on insulin compared with those on metformin. Nonetheless, these results should be viewed with caution because of potential confounding by indication, as insulin treatment could have been used simply because the diabetes was more severe. In keeping with this hypothesis, another study found that insulin infusion allowed achievement of glycaemic targets and improved outcomes in patients with hyperglycaemia with COVID-19.[18]

Despite better outcomes reported in patients with COVID-19 with diabetes treated with metformin,[28] the drug should be stopped in patients with respiratory distress, renal impairment, or heart failure[90] because of a risk of lactic acidosis. A favourable effect of metformin in patients with COVID-19 has been hypothesised as the drug might prevent virus entry into target cells via adenosine monophosphate-activated protein kinase activation and the phosphatidylinositol-3-kinase–protein kinase B–mammalian target of rapamycin signalling pathway.[91]

A hypothetical anti-viral effect of SGLT2-inhibitors has also been suggested as these agents can decrease intracellular pH and increase lactate concentrations that could reduce the viral load.[92] Nonetheless, SGLT2 inhibitors require optimal hydration to avoid hypovolemia and electrolyte imbalance, and proper adjustment of insulin doses because of the risk of diabetic ketoacidosis.

GLP-1 receptor agonists might aggravate anorexia and should be discontinued in severely ill patients with COVID-19 because of a potential risk of aspiration pneumonia.[90] Nonetheless, their associated anti-inflammatory actions[93] and lung protection should be evaluated since preclinical studies have suggested that GLP-1 receptor agonists might attenuate pulmonary inflammation and preserve lung function in rats with experimental lung injury[94] and respiratory syncytial virus infection.[95]

DPP-4 inhibitors are associated with a low risk of hypoglycaemia and can be used for a wide renal function range. DPP-4 inhibitors are generally well tolerated and, in experimental studies, they were shown to mitigate inflammatory response.[96] Because soluble DPP-4 might act as a co-receptor for a subset of coronaviruses,[97] DPP-4 inhibitors might interfere with and modify such binding and hypothetically reduce virulence.[98] However, there is no clinical evidence of such an advantage and in two studies[23,28] no association was found between individual glucose-lowering drugs and outcomes. Because of the risk of hypoglycaemia, sulfonylureas should be stopped in

patients with diabetes with COVID-19, particularly if oral intake is poor or chloroquine is simultaneously used.[99]

Pioglitazone has anti-inflammatory properties, and in experimental animal models it reduced lung inflammation and fibrosis.[100,101] Nonetheless, the use of pioglitazone in patients with diabetes with COVID-19 is controversial because of the risk of fluid retention and oedema in haemodynamically unstable patients.

Therapies for COVID-19 in people with diabetes

Medical teams should ensure adequate glycaemic control in patients with diabetes with COVID-19. This requires considering all potential implications that therapies for COVID-19 might generate when used in patients with diabetes.

Treatment with chloroquine or hydroxychloroquine can cause hypoglycaemia, particularly in patients on insulin or sulfonylureas, because of their effects on insulin secretion, degradation, and action.[99] Conversely, antiviral drugs such as lopinavir and ritonavir could lead to hyperglycaemia and worsen glycaemic control.[102] These agents can cause hepatic and muscle toxicity so caution is recommended when they are used in combination with statins and in patients with fatty liver disease.[103] Pharmacokinetic interactions with antidiabetic drugs are also common, causing over-exposure or under-exposure to either antivirals or anti-diabetic drugs.[104]

Glucocorticoids have been used in patients with COVID-19 with severe acute respiratory distress syndrome as symptomatic and anti-inflammatory treatment. Their use, however, can worsen insulin resistance, sustain gluconeogenesis, worsen glycaemic control, and cause marked hyperglycaemia. As known, glucocorticoids exert their hyperglycaemic effects by reducing insulin sensitivity and insulin secretion, and also by interfering with GLP-1 effects, and enhancing production of glucagon.

Discussion

People with diabetes with COVID-19 are at a greater risk of worse prognosis and mortality. Given the high worldwide prevalence of diabetes, these individuals represent a large vulnerable segment of the COVID-19 population. The poorer prognosis of people with diabetes is the likely consequence of the syndromic nature of the disease (figure): hyperglycaemia, older age, comorbidities, and in particular hypertension, obesity, and cardiovascular disease all contribute to increase the risk in these individuals. The picture, however, is more complicated as it requires factoring in societal factors such as deprivation and ethnicity as well as factors that become relevant at the time that a patient with severe COVID-19 needs to be managed. Here, a physician has to account for not only the health status of the person with diabetes but also to balance carefully glucose-lowering treatments with specific treatments for the viral infection.

Once again, diabetes management in patients with COVID-19 poses a great clinical challenge, one that requires a much-integrated team approach, as this is an indispensable strategy to reduce the risk of medical complications and death as much as possible. Careful assessment of the many components that contribute to poor prognosis with COVID-19 in patients with diabetes might represent the best, if not the only way to overcome the current situation and enable our health systems to be ready to face any future challenges in a prompt and effective manner.

	Advantages	Disadvantages	Interactions with COVID-19 treatments
Metformin	No risk of hypoglycaemia	Risk of lactic acidosis in case of respiratory distress. Renal impairment. Heart failure	Lopinavir
DPP-4 inhibitors	No risk of hypoglycaemia. Available for a wide renal function range. Potential anti-inflammatory action. Potential modification of SARS-CoV-2 binding to DPP-4	N/A	Lopinavir/ritonavir; Atazanavir
SGLT2-inhibitors	No risk of hypoglycaemia	Risk of hypovolemia. Electrolyte imbalances. Euglycaemic ketoacidosis	Lopinavir/ritonavir
GLP-1 receptor agonists	No risk of hypoglycaemia. Potential anti-inflammatory action	Risk of gastrointestinal side-effects and aspiration	Atazanavir
Sulfonylureas	N/A	Risk of hypoglycaemia if oral intake is administered with other glucose-lowering agents	Lopinavir/ritonavir; Hydroxychloroquine
Pioglitazone	Anti-inflammatory action	Risk of fluid retention and heart failure	Favipiravir
Insulin	Recommended in critical patients	Risk of hypoglycaemia. Possible need for high doses. Intravenous administration	Hydroxychloroquine

Usual at home antidiabetic therapy can be maintained in patients receiving treatment in hospital with regular caloric and fluid intake according to the clinical status, risk of drug-related adverse effects, and interactions between antidiabetic agents and drugs used for the treatment of COVID-19. However, insulin is the preferred agent for glycaemic control in patients with diabetes receiving treatment in hospital, and its use is mandatory in critically ill patients. N/A=not applicable.

Table 3: **Antidiabetic treatment during COVID-19**

Search strategy and selection criteria

We searched PubMed for articles using the search terms "diabetes mellitus", "Type 1 diabetes mellitus", "Type 2 diabetes mellitus", "new onset diabetes", "outcome", "age", "gender", "ethnicity", "comorbidities", "hypertension", "cardiovascular disease", "obesity", "inflammation", "coagulation", "hyperglycaemia", "ketoacidosis" , "anti-diabetic drug", "ACE-inhibitors", and "hydroxychloroquine", in conjunction with the terms "COVID-19" and "SARS-CoV-2 infection". No criteria for publication data were set, and all articles in English were included if published before June 30, 2020. We also checked reference lists in relevant articles and Google Scholar for additional references.

Finally, the inter-relationship between diabetes and COVID-19 should trigger more research to understand the extent to which specific mechanisms of the virus (eg, its tropism for the pancreatic β-cell) might contribute to worsening of glycaemic control and, in some cases, to the striking development of diabetic ketoacidosis or hyperglycaemic hyperosmolar syndrome, and possibly the development of new-onset diabetes.

Contributors

MA, MCC, MM, and LM contributed equally to this manuscript preparation by doing the literature search, critically selecting data from the literature, writing the manuscript draft, and preparing tables and drawing figures. AC and SDP designed the review structure and literature search, and finalised the manuscript.

Declaration of interests

SDP reports grants and personal fees from AstraZeneca, Boheringer Ingelheim, and Novartis Pharmaceuticals; and personal fees from Eli Lilly, GlaxoSmihKline, Janssen, Novo Nordisk A/S, Laboratoires Servier, Sanofi, and Takeda Pharmaceuticals. All other authors declare no competing interests.

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References

1 Healthmap. Novel coronavirus (COVID-19). https://www.healthmap.org/covid-19/ (accessed June 7, 2020).

2 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; published online Feb 24. https//:doi.org.10.1001/jama.2020.2648.

3 Zhang Y, Cui Y, Shen M, et al. Association of diabetes mellitus with disease severity and prognosis in COVID-19: a retrospective cohort study. *Diabetes Res Clin Pract* 2020; **165:** 108227.

4 Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr Clin Res Rev* 2020; **14:** 535–45.

5 Booth CM. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003; **289:** 2801–09.

6 Shi Q, Zhang X, Jiang F, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. *Diabetes Care* 2020; **43:** 1382–91.

7 Williamson E, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. *J Chem Inf Model* 2019; **53:** 1689–99.

8 Garbati MA, Fagbo SF, Fang VJ, et al. A comparative study of clinical presentation and risk factors for adverse outcome in patients hospitalised with acute respiratory disease due to MERS coronavirus or other causes. *PLoS One* 2016; **11:** e0165978

9 Schoen K, Horvat N, Guerreiro NFC, de Castro I, de Giassi KS. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. *BMC Infect Dis* 2019; **19:** 964.

10 Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. *Eur Respir J* 2020; **55:** 2000547

11 Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020; **109:** 531–38.

12 Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. *J Endocrinol Invest* 2020; **43:** 867–69.

13 Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. *BMJ* 2020; published online April 11. https//:doi.org.10.1101/2020.04.08.32444366.

14 Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. *J Clin Virol* 2020; **127:** 104354.

15 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395:** 1054–62.

16 Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab* 2020; **31:** 1068–77.

17 Yan Y, Yang Y, Wang F, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. *BMJ Open Diabetes Res Care* 2020; published online April 8. https//:doi.org.10.1136/bmjdrc-2020-001343.

18 Sardu C, D'Onofrio N, Balestrieri ML, et al. Outcomes in patients with hyperglycemia affected by Covid-19: can we do more on glycemic control? *Diabetes Care* 2020; **43:** 1408–15.

19 Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: a systematic review and meta-analysis. *Int J Infect Dis* 2020; **94:** 91–95.

20 Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020; published online Aug 13. https://doi.org/10.1016/S2213-8587(20)30272-2.

21 Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020; published online March 31. https//:doi.org.10.1002/dmrr.3319.

22 EpiCentro. Portale di epidemiologia per gli operatori sanitari. https://www.epicentro.iss.it/ (accessed May 20, 2020).

23 Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* 2020; published online May 29. https//:doi.org.10.1007/s00125-020-05180-x.

24 Holman N, Knighton P, Kar P, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020; published online Aug 13. https://doi.org/10.1016/S2213-8587(20)30271-0.

25 Ebekozien OA, Noor N, Gallagher MP, Alonso GT. Type 1 diabetes and COVID-19: preliminary findings from a multicenter surveillance study in the US. *Diabetes Care* 2020; published online June 5. https//:doi.org.10.2337/dc20-1088.

26 Dudley JP, Lee NT. Disparities in age-specific morbidity and mortality from SARS-CoV-2 in China and the Republic of Korea. *Clin Infect Dis* 2020; published online March 31. https//:doi.org.10.1093/cid/ciaa354.

27 The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *China CDC Wkly* 2020; **2:** 113–22.

28 Chen Y, Yang D, Cheng B, et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. *Diabetes Care* 2020; **43:** 1399–407.

29 Haynes N, Cooper LA, Albert MA, Association of Black Cardiologists. At the heart of the matter: unmasking and addressing COVID-19's toll on diverse populations. *Circulation* 2020; published online May 4. https//:doi.org.10.1161/CIRCULATIONAHA.120.048126.

30 The Washington Post. https://www.washingtonpost.com/nation/2020/04/07/coronavirus-is-infecting-killing-black-americans-an-alarmingly-high-rate-post-analysis-shows/?arc404=true (accessed May 21, 2020).

31 Coronavirus Resource Center, Johns Hopkins University and Medicine. https://coronavirus.jhu.edu/map.html (accessed June 4, 2020).

32 Jüni P, Rothenbühler M, Bobos P, et al. Impact of climate and public health interventions on the COVID-19 pandemic: a prospective cohort study. *CMAJ* 2020; **192:** 566–73.

33 Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020; **97:** 829–38.

34 Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis* 2020; **94:** 91–95.

35 Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci* 2020; **63:** 457–60.

36 Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203:** 631–37.

37 Arendse LB, Jan Danser AH, Poglitsch M, et al. Novel therapeutic approaches targeting the renin-angiotensin system and associated peptides in hypertension and heart failure. *Pharmacol Rev* 2019; **71:** 539–70.

38 Igase M, Strawn WB, Gallagher PE, Geary RL, Ferrario CM. Angiotensin II AT1 receptors regulate ACE2 and angiotensin–(1–7) expression in the aorta of spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol* 2005; **289:** 533–39.

39 Ohnishi ET, Murakami K. Renin–angiotensin system research: from molecules to the whole body. *J Physiol Sci* 2019; **69:** 581–87.

40 Caldeira D, Alarcão J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ* 2012; **345:** e4260.

41 Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–angiotensin–aldosterone system blockers and the risk of Covid-19. *N Engl J Med* 2020; **382:** 2431–40.

42 Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect* 2020; **9:** 757–60.

43 Reynolds HR, Adhikari S, Pulgarin C, et al. Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. *N Engl J Med* 2020; **382:** 2441–48.

44 Kim IC, Kim JY, Kim HA, Han S. COVID-19-related myocarditis in a 21-year-old female patient. *Eur Heart J* 2020; **41:** 1859.

45 Sala S, Peretto G, Gramegna M, et al. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. *Eur Heart J* 2020; **41:** 1861–62.

46 Buja LM, Wolf D, Zhao B, et al. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. *Cardiovasc Pathol* 2020; **48:** 107233.

47 Li JW, Han TW, Woodward M, et al. The impact of 2019 novel coronavirus on heart injury: a systemic review and meta-analysis. *Prog Cardiovasc Dis* 2020; published online April 16. https//:doi.org.10.1016/ j.pcad.2020.04.008.

48 Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: possible mechanisms. *Life Sci* 2020; **253:** 117723.

49 Caussy C, Pattou F, Wallet F, et al. Prevalence of obesity among adult inpatients with COVID-19 in France. *Lancet Diabetes Endocrinol* 2020; **8:** 562–64.

50 Sattar N, McInnes IB, McMurray JJ V. Obesity a risk factor for severe COVID-19 infection: multiple potential mechanisms. *Circulation* 2020; published online April 22. https//:doi.org.10.1161/CIRCULATIONAHA.120.047659.

51 Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity* 2020; **28:** 1195–99.

52 Connors J, States U, Levy J, States U. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020; **135:** 2033–40.

53 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020; **18:** 1094–99.

54 Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med* 2020; published online May 6. https//:doi.org.10.7326/M20-2003.

55 Zhao L. Obesity accompanying COVID-19: the role of epicardial fat. *Obesity* 2020; published online May 4. https//:doi.org.10.1002/oby.22867.

56 Nagy E, Jermendy AL, Merkely B, Maurovich-Horvat P. Clinical importance of epicardial adipose tissue. *Arch Med Sci* 2017; **13:** 864–74.

57 Zheng KI, Gao F, Wang X-B, et al. Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. *Metabolism* 2020; **108:** 154244.

58 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of non-alcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64:** 73–84.

59 Lei F, Liu YM, Zhou F, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. *Hepatology* 2020; published May 2. https//:doi.org.10.1002/hep.31301.

60 Zippi M, Sirio F, Occhigrossi G, Hong W. Hypertransaminasemia in the course of infection with SARS-CoV-2: incidence and pathogenetic hypothesis. *World J Clin Cases* 2020; **8:** 1385–90

61 Mitchell F. Vitamin-D and COVID-19: do deficient risk a poorer outcome? *Lancet Diabetes Endocrinol* 2020; **8:** 570.

62 Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395:** 507–13.

63 Palm NW, Medzhitov R. Not so fast: adaptive suppression of innate immunity. *Nat Med* 2007; **13:** 1142–44.

64 Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab* 2020; **318:** e736–41.

65 Kyriazopoulou E, Leventogiannis K, Norrby-Teglund A, et al. Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis. *BMC Med* 2017; **15:** 172.

66 Henry BM, Helena M, Oliveira S De, Benoit S. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* 2020; **58:** 1021–28.

67 Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8:** 420–22.

68 Chen Y, Feng Z, Diao B, et al. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes. *medRxiv* 2020; published online March 31. https//:doi.org.10.1101/2020.03.27.20045427.

69 Diao B, Feng Z, Wang C, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *medRxiv* 2020; published online April 10. https//:doi.org.10.1101/2020.03.04.20031120.

70 Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020; published online Feb 19. https//:doi.org.10.1111/all.14238.

71 Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; published online March 13. https//:doi.org.10.1001/jamainternmed.2020.0994.

72 Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; **130:** 2620–29.

73 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020; **18:** 844–47.

74 Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020; published online May 21. https//:doi.org.10.1056/NEJMoa2015432.

75 McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol* 2020; **2:** e437–45.

76 Dunn E, Grant P. Type 2 diabetes: an atherothrombotic syndrome. *Curr Mol Med* 2005; **5:** 323–32.

77 Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020; published online April 12. https//:doi.org.10.1016/j.jaci.2020.04.006.

78 Scheen AJ, Marre M, Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: findings from the CORONADO study and other recent reports. *Diabetes Metab* 2020; published online May 21. https//:doi.org.10.1016/j.diabet. 2020.05.008.

79 Pornet C, Bourdel-Marchasson I, Lecomte P, et al. Trends in the quality of care for elderly people with type 2 diabetes: the need for improvements in safety and quality (the 2001 and 2007 ENTRED surveys). *Diabetes Metab* 2011; **37:** 152–61.

80 Iacobellis G, Penaherrera CA, Bermudez LE, Bernal Mizrachi E. Admission hyperglycemia and radiological findings of SARS-COV-2 in patients with and without diabetes. *Diabetes Res Clin Pract* 2020; **164:** 108185.

81 Zhang Y, Li H, Zhang J, et al. The clinical characteristics and outcomes of patients with diabetes mellitus and secondary hyperglycaemia with coronavirus disease 2019: a single-center, retrospective, observational study in Wuhan. *Diabetes Obes Metab* 2020; published online May 14. https//:doi.org.10.1111/dom.14086.

82 Li H, Tian S, Chen T, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. *Diabetes Obes Metab* 2020; published online May 29. https://doi.org.10.1111/dom.14099.

83 Wang F, Yang Y, Dong K, et al. Clinical characteristics of 28 patients with diabetes and COVID-19 in Wuhan, China. *Endocr Pract* 2020; **26:** 668–74.

84 Bode B, Garrett V, Messler J, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. *J Diabetes Sci Technol* 2020; **14:** 813–21.

85 Rayman G, Lumb A, Kennon B, et al. Guidance on the management of diabetic ketoacidosis in the exceptional circumstances of the COVID-19 pandemic. *Diabet Med* 2020; **37:** 1214–16.

86 Kim NY, Ha E, Moon JS, Lee Y-HH, Choi EY. Acute hyperglycemic crises with coronavirus disease-19: case reports. *Diabetes Metab J* 2020; **44:** 349–53.

87 Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab* 2020; published online April 20. https//:doi.org.10.1111/dom.14057.

88 Sobngwi E, Choukem SP, Agbalika F, et al. Ketosis-prone type 2 diabetes mellitus and human herpesvirus 8 infection in sub-Saharan Africans. *JAMA* 2008; **299:** 2770–76.

89 Jie Chee Y, Jia Huey Ng S, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res Clin Pract* 2020; **164:** 108166.

90 Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; **8:** 546–50.

91 Sharma S, Ray A, Sadasivam B. Metformin in COVID-19: a possible role beyond diabetes. *Diabetes Res Clin Pract* 2020; **164:** 108183.

92 Cure E, Cumhur Cure M. Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. *Diabetes Metab Syndr Clin Res Rev* 2020; **14:** 405–06.

93 Mazidi M, Karimi E, Rezaie P, Ferns GA. Treatment with GLP1 receptor agonists reduce serum CRP concentrations in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *J Diabetes Complications* 2017; **31:** 1237–42.

94 Viby NE, Isidor MS, Buggeskov KB, Poulsen SS, Hansen JB, Kissow H. Glucagon-like peptide-1 (GLP-1) reduces mortality and improves lung function in a model of experimental obstructive lung disease in female mice. *Endocrinology* 2013; **154:** 4503–11.

95 Bloodworth MH, Rusznak M, Pfister CC, et al. Glucagon-like peptide 1 receptor signaling attenuates respiratory syncytial virus–induced type 2 responses and immunopathology. *J Allergy Clin Immunol* 2018; **142:** 683–87.

96 Sun Q, Zhang Y, Huang J, et al. DPP4 regulates the inflammatory response in a rat model of febrile seizures. *Biomed Mater Eng* 2017; **28:** S139–52.

97 Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* 2013; **495**: 251–4.

98 Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? *Diabetes Res Clin Pract* 2020; **162:** 108125.

99 Unübol M, Ayhan M, Guney E. Hypoglycemia induced by hydroxychloroquine in a patient treated for rheumatoid arthritis. *J Clin Rheumatol* 2011; **17:** 46–47.

100 Aoki Y, Maeno T, Aoyagi K, et al. Pioglitazone, a peroxisome proliferator-activated receptor gamma ligand, suppresses bleomycin-induced acute lung injury and fibrosis. *Respiration* 2009; **77:** 311–19.

101 Barbarin V, Nihoul A, Misson P, et al. The role of pro- and anti-inflammatory responses in silica-induced lung fibrosis. *Respir Res* 2005; **6:** 112.

102 Paengsai N, Jourdain G, Salvadori N, et al. Recommended first-line antiretroviral therapy regimens and risk of diabetes mellitus in HIV-infected adults in resource-limited settings. *Open Forum Infect Dis* 2019; **6:** 1–7.

103 Bruno R, Sacchi P, Maiocchi L, Patruno S, Filice G. Hepatotoxicity and antiretroviral therapy with protease inhibitors: a review. *Dig Liver Dis* 2006; **38:** 363–73.

104 Liverpool COVID-19 interactions. https://www.covid19-druginteractions.org/ (accessed May 5, 2020).