Interactions between diabetes and COVID-19: A narrative review

Sophia Sabri, Olivier Bourron, Franck Phan, Lee S Nguyen

ORCID number: Sophia Sabri 0000-0002-6014-6261; Olivier Bourron 0000-0001-7348-7161; Franck Phan 0000-0002-1412-9687; Lee S Nguyen 0000-0002-6014-6269.

Author contributions: Sabri S wrote the manuscript; Bourron O and Phan F cowrote the manuscript; Bourron O, Phan F and Nguyen LS provided expertise; and Nguyen LS supervised this work.

Conflict-of-interest statement: All other authors have nothing to disclose.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Endocrinology and metabolism

Country/Territory of origin: France

Abstract

Diabetes, whether due to pancreatic beta cells insufficiency or peripheral resistance to insulin, has been suggested as a risk factor of developing severe acute respiratory disease coronavirus-2 (SARS-CoV-2) infections. Indeed, diabetes has been associated with a higher risk of infections and higher risk of developing severe forms of coronavirus disease 2019 (COVID-19) related pneumonia. Diabetic patients often present associated comorbidities such as obesity, hypertension and cardiovascular diseases, and complications of diabetes, including chronic kidney disease, vasculopathy and relative immune dysfunction, all of which make them more susceptible to infectious complications. Moreover, they often present low-grade inflammation with increased circulating interleukin levels, endothelial susceptibility to inflammation and dysfunction, and finally, hyperglycemia, which increases this risk. Additionally, corticosteroids, which count among the few medications which showed benefit on survival and mechanical ventilation requirement in COVID-19 pneumonia in large randomized controlled trials, are associated to new onsets of diabetes, and metabolic disorders in patients with previous history of diabetes. Finally, SARS-CoV-2 via the alternate effects of the renin-angiotensin system, mediated by the angiotensin-converting-enzyme 2, was also associated with insulin resistance in key tissues involved in glucose homeostasis, such as liver, skeletal muscles, and adipose tissue; and also, with impaired insulin secretion by pancreatic β-cells. In this work, we reviewed all elements which may help understand how diabetes affects patients with COVID-19, how treatments affect outcomes in patients with COVID-19, how they may cause new onsets of diabetes, and finally review how SARS-CoV-2 may inherently be a risk factor of developing diabetes, through immune-mediated diabetogenic mechanisms.
INTRODUCTION

Preexisting diabetes and coronavirus disease 2019

Preexisting diabetes is associated with poor outcomes of coronavirus disease 2019: There is a set of arguments to say that patients with diabetes are at high risk of severe form of coronavirus disease 2019 (COVID-19) pneumonia. Quickly, at the start of the epidemic, reports from China and Italy suggested that diabetes rate ratio was two or three-fold in patients with more severe than in those with less severe infections[1-5]. Patients with diabetes and COVID-19 pneumonia were more likely to require intensive care, present organ failure, hypercoagulability state with increased levels of inflammatory factors[1,3,6]. In terms of absolute risk, three people with diabetes in every 1000 developed fatal or critical care unit-treated COVID-19[7]. In the French COVID CORONADO cohort, only 50% of the 2796 patients with diabetes were discharged and 20% died within 28 d after hospitalization, reflecting the severity of the disease in the diabetic population[8]. In other countries, mortality rate of patients with diabetes and COVID-19 during the first wave was between 11% and 33%[9-11]. In a retrospective study of 7337 cases of COVID-19 in China, 952 patients with pre-existing type 2 diabetes (T2D) required more medical interventions and presented multiple organ failure than non-diabetic individuals[6]. In this study, T2D was significantly associated with the incidence of acute respiratory distress syndrome (ARDS), septic shock, and acute kidney injury with respective adjusted hazard ratios (HR) of 1.44 (95%CI: 1.20-1.73), 1.95 (95%CI: 1.18-3.20) and 3.01 (95%CI: 1.94-4.68). These findings explain the high mortality rate observed in this population. In Italy, for example, a third of people who died from COVID during the first wave were diabetic[12]. In March 28th, 2020, 2112 deaths from confirmed COVID-19 cases were reported to CDC and diabetes was one of the more frequently reported conditions among all cases. Indeed, a third of the patients hospitalized in intensive care had diabetes[13]. On the other hand, the prevalence of diabetes in non-hospitalized patients among COVID-19 patients was 6%, less than the prevalence of diabetes among United States adults estimated to 10.1% [14]. This may suggest that diabetes is more a risk factor of severity in case of COVID-19 than a risk factor of COVID-19 itself. Data from New York hospitals also found a significantly increased risk of severe forms associated with diabetes, which however disappeared after adjusting for potential confounding factors[15-17]. All data converge to say that diabetes is associated with severe forms of COVID-19, but other factors may impact this association. Diabetic patients constitute a very heterogeneous population, in terms of type of diabetes, disease duration, quality of glycemic control, presence of diabetic complications, antidiabetic treatment used, presence of comorbidities such as obesity, hypertension, dyslipidemia, tobacco and cardiovascular diseases. Yet, only
few studies accounted for these potential confounders.

Are patients with diabetes at risk of severe form of COVID-19?

Impact of age in morbi-mortality of COVID-19 in patients with diabetes: As T2D is more prevalent in elderly patients, whether it is a risk factor of COVID-19 independent from age is currently unknown. Cohort studies in COVID-19 patients which focused on patients with T2D, yielded a mean age between 62 (55-68) in China, and 69.8 ± 13.0 in the French nationwide multicenter CORONADO study[8,18]. The latter study aimed to determine predictors of discharge from hospital and death within 28-d after hospital admission in patients with diabetes and COVID-19. After multiple adjustments, older age and history of microvascular complications were associated with most associated with poor outcomes.

In a systematic review and meta-analysis which included observational studies and investigated risk phenotypes of diabetes and association with COVID-19 severity and deaths, older age (> 65 years) was associated with a 3.49 higher relative risk of COVID-19-related death (95%CI: 1.82-6.69)[19]. Several studies have also shown the absence of excess mortality in young or middle aged patients with type 1 diabetes (T1D)[8,20].

Impact of diabetic complications in morbi-mortality of COVID-19: As the organs affected by COVID-19 are the same affected by diabetes, a relevant question which quickly rose was whether diabetes-induced organ injuries impacted COVID-19 severity. In the French CORONADO study, microvascular complications were associated with a greater risk of death[8]. In a Scottish register study, microvascular complications such as retinopathy and nephropathy were also significantly associated with developing fatal or critical care unit-treated COVID-19[7]. In a population-based cohort study of people with diabetes, increased COVID-19-related mortality was associated with cardiovascular and renal complications of diabetes[21]. Diabetic patients with related chronic kidney disease were even more at risk, in a meta-analysis, with a relative risk of COVID-19-related mortality of 2.53 (95%CI: 0.93-6.88) [19].

Impact of type of diabetes and prognosis of COVID-19: Data about T1D are scarce and contradictory due to the heterogeneous study populations and the presence of many limitations. The French CORONADO study showed a low prevalence of T1D among patients with diabetes hospitalized for COVID-19, 2.1%, lower than that expected in the general population. Data also suggested a lower risk of severe prognosis in patients hospitalized with T1D and COVID-19 than in those with T2D, with half the risk of death by day 7. In a Belgian cohort study, risk of hospitalization was similar in 2336 patients with T1D, compared to 15239 normoglycemic individuals (0.21% vs 0.17%)[20]. In a large British population cohort study, including 61 million individuals, showed that patients with T1D (n = 263830; 0.4%) presented an increased risk of in-hospital death due to COVID-19 compared with those without known diabetes [OR: 3.50 (95%CI: 3.15-3.89)][22]. In this study, mortality was higher in T1D than in T2D patients. Even then, age represented a risk factor in T1D patients. In the Belgian cohort, those hospitalized for COVID-19 were older [66 years (58-80) vs 49 years (35-61), P = 0.010]. Moreover, similarly as in the British study, in the French CORONADO study, no deaths in young patients with T1D (less than 50-55 years old) was reported. In addition, children and adolescents with T1D showed similar risk of infection and subsequent mortality than those without T1D in several cohorts, which emphasize this age-related risk of being infected and developing severe forms of COVID-19 pneumonia in patients with T1D[23,24].

Obesity, an added risk factor of COVID-19 severity: Obesity is highly prevalent in patients hospitalized for COVID-19 and has also been identified as an independent risk factor for the severity of the disease[25]. Obesity and diabetes, especially T2D, are two commonly associated diseases that are supported by epidemiological as well as genetic studies. One study assessed the relationship between obesity classes and COVID-19 prognosis in patients with T2D. Among 1965 patients with T2D, intubation for mechanical ventilation and death were significantly and independently increased in overweight patients [OR: 1.65 (95%CI: 1.05-2.59)], in patients with class I obesity [OR: 1.93 (95%CI: 1.19-3.14)] and class II/III obesity [OR: 1.98 (95%CI: 1.11-3.52)]. In a prospective, community-based, cohort study among 6910695 individuals, a linear increase in risk of severe COVID-19 leading to admission to hospital and death was observed. This risk increase was superior to that expected to diabetes only. The relative risk due to increasing body mass index was greater in people younger than 40 years and African origins[26]. Hence, T2D combined with obesity may be a synergic risk factor of severe COVID-19 pneumonia. Yet it has to be noted that obesity does not
Impact mortality as much in in elderly patients[27].

Influence of glycemic control on the prognosis of COVID-19: A key question is the role of hyperglycemia in patients with diabetes and COVID-19. This question must be analyzed differently depending on whether one considers the time before hospitalization on admission or during the hospitalization phase. Results on glycemic control before hospitalization are contradictory. A major result of the CORONADO study is that glycemic control prior to hospitalization, assessed by the dosage of glycated hemoglobin (HbA1c), does not seem to have a significant impact on the severity of COVID-19 in people with diabetes who are hospitalized. On the contrary, in a population-based cohort study of people with diagnosed diabetes in England, people with T2D had a higher COVID-19-related mortality when HbA1c was superior to 59 mmol/mol (76%) in comparison to an HbA1c in the range 48-53 mmol/mol (65%-70%). In patients with T2D, this between-group difference was more pronounced in those under 70 than in those over 70 years-old. No significant difference was observed for HbA1c and risk of severe form of COVID-19 in patients with T1D[8,21].

On the other hand, association between hyperglycemia at the time of admission and mortality due to COVID-19 is clearer. Sardu et al[28] found that a glycaemia > 7.7 mmol/L on admission was associated with outcome in 132 Italian hyperglycemic patients hospitalized for COVID-19 pneumonia. In a Chinese retrospective multicenter study including hospitalized patients with COVID-19, well-controlled glycaemia (defined as a glycemic variability between 3.9 to 10.0 mmol/L) was associated with markedly lower mortality compared to individuals with poorly controlled glycaemia (upper limit of glycemic variability exceeding 10.0 mmol/L) (adjusted HR: 0.14)[6]. In a retrospective study among patients with diabetes and COVID-19 with use of continuous glucose monitoring, both glucose levels of > 8.8 mmol/L and < 3.85 mmol/L were associated with a significantly high risk of composite adverse outcomes of COVID-19 [i.e., need for admission to the intensive care unit (ICU), for mechanical ventilation, for vasopressor-requiring hypotension, multiple organ dysfunction] as well as with a prolonged hospitalization. Higher glycemic variability on admission was also significantly associated with a poorer outcome of COVID-19[29,30]. In contrast, mean sensor glucose level was not significantly associated with morbidity[30].

While hyperglycemia on admission was associated with severe outcomes, question of causality remains elusive. Although Sardu et al[28] showed that the greater the decrease in blood glucose the better the outcomes were, in their observational study, causal relationship between correction of hyperglycemia and better prognosis could not be ascertained. In other settings than COVID-19, glycaemia on admission may be used as a biomarker to identify patients at higher risk of severe pneumonia[31,32]. Hence, randomized controlled studies are still needed to definitely answer this causality question.

What is the link between diabetes and the risk of severe form of COVID-19?
There are many hypotheses about the mechanism of how diabetes affects COVID-19 course.

Hyperglycaemia and diabetes are associated with higher risk of infectious diseases:
Infectious diseases, including pneumonia are leading causes of death in people with diabetes[33-35]. Specifically, diabetes was previously proven a major risk factor of mortality related to other viruses than severe acute respiratory disease coronavirus-2 (SARS-CoV-2), such as influenza A (H1N1) influenzae or the Middle East respiratory syndrome-related coronavirus (MERS-CoV)[36,37]. Mechanisms of susceptibility towards severe viral infections include neutrophil dysfunction and disturbance in the adaptive immune response in hyperglycemic environment[38-40]. As a matter of fact, hyperglycaemia in itself, was associated with immune system impairment, complement fixation or altered cytokines and chemokines production enhancing SARS-CoV-2 replication[38,41-43]. However, severe forms of COVID-19 pneumonia in patients with hyperglycemia do not appear to result from an impaired humoral response against SARS-CoV-2[44]. These elements may explain the observations of improved prognosis associated with better blood glucose control in hospitalized patients with COVID-19, mentioned before.

Altered immune response and hyperinflammation in patients with diabetes and COVID-19: Histopathologic analysis revealed in fatal COVID-19 patients the presence of massive inflammatory cell infiltration in many organs such as lung, myocardial, liver, brain and nerves, kidney and pancreas[45]. Indeed, cytokines are secreted in
great abundance and increased levels of inflammatory cytokines were associated with increased mortality in patients hospitalized for severe COVID-19 pneumonia. Among them, interleukin-6 (IL-6), also associated with cytokine release syndrome, is usually associated with diabetes, and denotes low-grade inflammation with circulating IL-6. Levels higher than in population without diabetes. Interestingly, study cohorts in patients admitted for severe COVID-19 pneumonia, showed higher levels of inflammation biomarkers including circulating IL-6, in patients with diabetes than other patients[46]. In T2D patients suffering from coronavirus infection, monocytopenia, morphological anomaly of increased monocyte size and CD8 T cells specific lymphopenia were observed[47]. The deregulation of innate and adaptive immune responses could lead to the hyperinflammation observed in severe COVID-19, especially in T2D patients. Visceral adipose tissue that is increased in patients with diabetes could represent a reservoir of cytokines and therefore could also explain the disproportionate inflammatory response observed in patients with diabetes and COVID-19.

Obesity and related disorders associated with the risk of severe forms of COVID-19: COVID-19 pneumonia may deteriorate in obese patients with diabetes due to poor respiratory mechanics. Indeed, when combining obesity and diabetes, patients present weaker respiratory muscle strength, reduced lung volume, increased resistance to the airways, impaired gas exchange, dysregulation of ventilatory control and bronchial dysautonomia[48-50]. Thus, COVID-19 severity could be more severe in case of pre-existing lung damage associated with obesity. Furthermore, in case of T2D and obesity, nonalcoholic fatty liver disease (NAFLD) is highly prevalent, and some data suggest that liver steatosis and higher stages of NAFLD (i.e., non-alcoholic steatohepatitis and liver fibrosis) would be a risk marker for SARS-CoV-2 infection severity[51]. Insulin resistance, a common pathophysiologic trait between obesity and T2D, could explain the increased risk of COVID-19 mortality in diabetes and obesity. Indeed, triglycerides and glucose index was closely associated with the severity and morbidity in COVID-19 patients[52]. In addition, complex interactions can occur between adipose tissue and the immune system[53]. Among them, hyperleptinemia and leptin resistance commonly observed in obesity, are implicated in the increased secretion of pro-inflammatory cytokines that sustain and enhance the inflammatory responses. Interestingly, hyperleptinemia and leptin resistance may aggravate clinical outcomes in infectious diseases, including H1N1 influenza but also COVID-19[54,55]. Adipose tissue can finally constitute a viral reservoir of SARS-CoV-2, exacerbating the severity of COVID-19 through amplification of immune and cytokine activation[56]. Indeed, SARS-CoV-2 has a high affinity to bind the angiotensin-converting enzyme 2 (ACE2) receptors, highly expressed in adipose tissue. Obese patients have more adipose tissue than lean individuals, resulting in more ACE2 receptors. However, association between obesity and viral load has not been confirmed[57]. In sum, it is difficult to date to distinguish the role of overweight or obesity on the severity of SARS-CoV-2 infections in patients with T2D mellitus (T2DM) and the diabetic state itself.

Thromboembolic risk is increased in people with diabetes and COVID-19: COVID-19 is associated with an increased risk of thromboembolic events. Although, as of yet, there is no evidence of increased risk of such events in patients with diabetes in the setting of COVID-19 infections, several publications reported an increased thromboembolic risk in patients with diabetes. In a large population-based study which included 56158 patients with T2D and 168474 control patients, T2D patients exhibited an increased risk of venous thromboembolism (HR: 1.44, 95% CI: 1.27-1.63). Furthermore, the risks of pulmonary embolism were greater in the patients with T2D than in the controls (HR: 1.52, 95% CI: 1.22-1.90)[58]. Interestingly, hyperglycemia potentiates coagulation, whereas hyperinsulinemia inhibits fibrinolysis, suggesting that T2D patients may be especially vulnerable to prothrombotic events during inflammatory states such as COVID-19[59].

Endothelial cell dysfunction is observed in patients with diabetes and COVID-19: Histopathologic studies in patients with COVID-19 revealed evidence of viral presence in endothelial cells, and endothelitis was found in vascular beds of multiple organs such as heart, kidney, lungs, small intestine, and liver[60]. Vascular endothelial dysfunction seem to contribute to the pathophysiology of SARS-CoV-2 infection, by causing inflammatory cell infiltration, endothelial cell apoptosis and microvascular prothrombotic effects[61]. Interestingly endothelial dysfunction also features in patients with diabetes[62]. Hence, infection of dysfunctional endothelial cell by SARS-CoV-2 may be additive to that of diabetes.
TREATMENTS, DIABETES AND COVID-19

Impact of antidiabetic treatments on COVID-19 prognosis

The question of the benefit/risk balance of anti-diabetic treatments in patients suffering from COVID-19 quickly arose during the first half of 2020. The benefits and risks of each antidiabetic treatment as well as the recommendation for their use during COVID-19 are summarized in Table 1.

Insulin: Insulin is often the recommended first-line anti-diabetic treatment in severe sepsis, especially if there is associated organ failure. Insulin infusion may be effective to achieve glycemic targets and improve outcomes in patients with COVID-19[28]. Although study design precluded causality analyses, patients with hyperglycemia treated with insulin infusion showed lower risk of severe disease than patients without insulin infusion. Meanwhile, other studies showed opposite results, with significant association between insulin treatment and a poorer prognosis of COVID-19 [8,63,64]. Remarkably, the association between insulin use and mortality was independent of patients’ age. Nevertheless, the worse outcome in patients under insulin may be related to a more severe and complicated overall state rather than a treatment effect. This treatment is also more frequently associated with glycemic variability, which has been associated with severe forms of COVID-19. Insulin treatment remains, until now, the standard treatment in diabetic patients with severe forms of COVID-19.

Dipeptidyl peptidase-4 inhibitors: Dipeptidyl peptidase-4 (DPP4) inhibitors modify the biological activity of substrates involved in the immune response to the infection and therefore could have potential benefit or harm in COVID-19 course. However, evidence from clinical trials on the association between the use of DPP4 inhibitors and the risk of community-acquired pneumonia in T2D patients did not show any increased risk[65]. Although ACE2 represents the main receptor, DPP4 might also bind to SARS-CoV-2[66]. Hence, DPP4 inhibition may play a role in antagonizing the DPP4/CD26, which interacts with the S1 domain of the viral spike glycoprotein, protein by which SARS-CoV-2 attaches to the ACE-2 receptor expressed on the cells surface[67]. Some studies showed better outcome in COVID-19 patients taking DDP-4 inhibitors, with less severe pneumonia and lower mortality risk[64]. However, in a large register study, covering almost the entire population of patients with type 2 diabetes and COVID in England, DPP-4 inhibitors had a higher risk of COVID-19 related mortality[63]. However, here again the existence of confounding bias doesn’t allow to conclude to a causal effect. Finally, a propensity score analysis from the CORONADO study concluded that use of DPP-4 inhibitors during the COVID-19 pandemic was safe and that they should not be discontinued[68].

Sodium/glucose cotransporter 2 inhibitors: Given the risk of ketoacidosis, especially in severe sepsis, some have recommended not to prescribe sodium/glucose cotransporter 2 inhibitors (SGLT-2is) in patients with COVID-19, since SGLT-2is are associated with an increased risk of ketoacidosis[69]. However, SGLT-2is could impact many processes dysregulated during COVID-19. For example, SGLT-2is reduced, in T2D patients, infiltration of inflammatory cells into arterial plaques and decreased the mRNA expression levels of some cytokines and chemokines, such as TNF, IL-6 and monocyte chemoattractant protein 1[70,71]. This pharmacological class also features significant cardiovascular and reno-protective benefits in cardiometabolic disease, and may provide similar organ protection in COVID-19. Khunti et al[63] showed, in a register study, that SGLT-2is are associated with a significant 18% mortality reduction due to COVID-19. DARE-19, a randomized, double-blind, placebo-controlled trial in 1250 patients is aiming to evaluate the safety and efficacy of dapagliflozin in addition to standard of care therapy in hospitalized patients with COVID-19 and high risk of severe form including T2D[72]. The full DARE-19 trial results will be presented shortly and could answer to the question of the usefulness of iSGLT-2 in COVID-19.

GLP-1 analogues: GLP-1 analogues (GLP-1a) could represent a good therapeutic alternative to treat T2D patients. First, targeting GLP-1 axis could improve many pathways dysregulated during COVID-19. Exendin-4 can reduce inflammation, macrophages activation and monocyte adhesion to endothelial cells and improve endothelial function[73,74]. Second, GLP-1a could ameliorate lung injury in animal models[75]. Furthermore, GLP-1a have cardiovascular and reno-protective properties that could be beneficial during SARS-CoV-2 infection. In the other hand, GLP-1a have been associated with increased ACE2 expression in lungs and heart tissue suggesting of possible helpful and harmful effects in COVID-19[76]. Khunti et al[63] have shown,
Table 1 Use of antidiabetic medications in patients with type 2 diabetes and coronavirus disease 2019

|                         | Insulin | Sulfonylurea | Metformin | DPP-4 inhibitors | SGLT-2is | GLP-1a |
|-------------------------|---------|--------------|-----------|------------------|----------|--------|
| Benefits                | Guarantee of achieving glycemic control; Cardiovascular neutrality; Possible use in multivisceral failure | Cardiovascular neutrality (demonstrated only with Glimepiride) | Probable cardiovascular benefit; No risk of hypoglycemia, improvement of inflammation and endothelial dysfunction | Cardiovascular neutrality; Possible use in severe renal impairment and hypoxia; Possible inhibitory role on the entry of the virus into the cell; No risk of hypoglycemia | Proven cardiovascular and renal protective benefits; No risk of hypoglycemia; Improvement of inflammation | Proven cardiovascular and renal protective benefits; Possibility of use up to the stage of severe renal failure; No risk of hypoglycemia; Improvement of inflammation and endothelial dysfunction |
| Risks                   | Increased glycaemic variability; Hypoglycaemic risks | Increased glycemic risk, contraindication in case of severe liver and renal failure | Multiple contraindications (hypoxia, severe renal failure, severe heart failure, severe liver failure); Risk of lactic acidosis especially in severe renal failure | Possible dysregulation of T cell function and T cell mediated inflammatory and immune responses | Reduced efficacy in moderate to severe renal impairment; Risk of ketoacidosis, especially in severe sepsis Risk of dehydration | Risk of digestive side effects; Risk of worsening undernutrition |
| Association with severe form of COVID-19 in observational studies | Conflicting results | Lower risk of severe form of COVID-19 or neutral association | Lower risk of severe form of COVID-19 or neutral association | Conflicting results | Lower risk of severe form of COVID-19 or neutral association | Neutral association |
| Medication use and severity of COVID-19 infection | Possibility of use at all stages of the disease and particularly in severe forms, especially recommended if blood sugar level is over 10-11 mM | Possible use up to moderate forms in the absence of severe renal and liver failure | Recommended use up to moderate forms in the absence of contraindications | Possible use up to moderate forms | Possible use up to moderate forms in the absence of moderate to severe renal failure | Possible use up to moderate forms |

COVID-19: Coronavirus disease 2019; DPP-4: Dipeptidyl peptidase-4; SGLT-2is: Sodium-glucose cotransporter-2 inhibitors; GLP-1a: Glucagon like peptide-1 analogues.

in a register study, that GLP-1a had a neutral effect for COVID-19-related death, as observed in the CORONADO study[8]. Although there is insufficient data to support the use of GLP-1a instead of insulin in patients with T2D and COVID-19, there is no evidence to discontinue them.

**Sulfonylureas:** Sulfonylureas are not associated with higher risk of COVID-19 mortality or are even sometimes associated with a lower risk[63]. However, no conclusion can be drawn since several biases exist in these studies. Indeed, use of sulfonylureas is limited in older and frailty people, in view of an increased risk of hypoglycemia.

**Metformin:** Many studies indicate that chronic metformin usage may have beneficial effects on COVID-19 with pre-existing T2D[19,63,77,78]. The findings of these studies could be related at least in part to confounding biases. Indeed, metformin is used early in the disease course of T2D, whereas other treatments such as insulin are initiated later or in case of contraindication to metformin such as renal failure. But surprisingly, benefits of metformin on COVID-19 outcomes occurred in spite of an apparently greater severity on admission compared with non-users[77]. Metformin could have beneficial effects on COVID-19 prognosis because of their protective properties on many cell types (e.g., endothelial cells, neurons and glial cells, cardiomyocytes, hepatocytes, macrophages)[79]. Activation of adenosine monophosphate-activated protein kinase pathways by metformin could also affect the expression of ACE2, the receptor for SARS-CoV-2[80]. Interestingly, one study have shown that metformin benefits would be greater in female patients with diabetes and COVID-19[81]. Besides COVID-19 setting, metformin use is also associated with a reduction in mortality from sepsis in diabetic patients hospitalized in intensive care units[82]. Although there is no direct evidence for a protective role of metformin in SARS-CoV-2 infection, some elements plead in favor of maintaining this treatment in the absence of contrain-
dication and in particular acute renal failure or hypoxia.

**Treatments against COVID-19: Corticosteroids**

COVID-19 pneumonia may various presentations, from the most benign cough to the most severe ARDS requiring venovenous extracorporeal membranous oxygenation. The pathophysiologic features of severe cases of COVID-19 are damages of the alveoli, inflammatory infiltrates, and microvascular circulation disorder leading to thrombosis. As previously stated, inflammatory organ injury may also, and multiples therapeutic have been suggested to decrease inflammatory organ injury but the effect of glucocorticoids has been debated.

Since the publication of results of the RECOVERY trial[83], all guidelines concur towards the use of corticosteroids in COVID-19 pneumonia: In patients hospitalized with COVID-19, use of dexamethasone resulted in lower 28-d mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization. Study protocol specified 6 mg of intravenous dexamethasone per day for 10 d. However, many patients are now treated at home, and French high council for public health recommended as alternative the use of methylprednisolone, 32 mg per day, or prednisone, 40 mg per day, or at very least the hydrocortisone at the dose of 160 mg for days (with decrease in 3 or 4 d), based on glucocorticoid equivalence, although results were less conclusive by oral route.

In a large meta-analysis, patients randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone were compared to those who received usual care or placebo[84]. Primary outcome was all-cause mortality at 28 d. This analysis included 1703 patients, with 5 trials which reported mortality at 28 d, 1 trial at 21 d, and 1 trial at 30 d. There were 222 deaths among 678 patients randomized to corticosteroids and 425 deaths among 1025 patients randomized to usual care or placebo [odds-ratio = 0.66 (95%CI: 0.53-0.82), P < 0.001], in agreement with RECOVERY. Hereafter, medical community acknowledged the usefulness of corticosteroids in treating COVID-19 patients. Yet, corticosteroids are associated with well-known side effects, one of which being steroid-induced diabetes, for which other risk factors may increase this risk of adverse reaction. Meanwhile, means to prevent steroid-induced diabetes also exist.

**Steroid-induced diabetes mellitus**

This entity is defined as an abnormal increase in blood glucose due to the treatment, in patients with or without previous history of diabetes. Thresholds are for 8-h fasting glucose: Above 7.0 mmol/L; after 2-h post-75 g oral glucose tolerance test: Above 11.1 mmol/L (2 g/L); HbA1c above 6.5%; or in symptomatic patients, a random plasma glucose above 11.1 mmol/L (2 g/L)[85]. Prevalence is estimated to between 18.6% and 25% of patients who use of corticosteroids daily[86]. In a meta-analysis which included 3407 non-diabetic patients treated with glucocorticoids, the incidence of hyperglycemia was 32.3% and that of diabetes was 18.6%[87].

Mechanisms are plural and mostly feature beta cell dysfunction and insulin resistance. Beta cell dysfunction participates to insulin insufficiently due to decreased systemic release, and decreased sensitivity to glucose. Insulin resistance occurs in the liver, skeletal muscle, and fat cells, leading to decreased intracellular signals mediated by insulin. From a molecular point of view, glucocorticoids use schematically leads to a decrease in phosphorylation of the protein kinase B (PKB), which in turn leads to a decrease in activity of the glucose transporters GLUT4, which are less translocated to the cell surface, hence, lead to insulin resistance and decrease in glucose uptake, particularly at the muscle and adipose tissue level[88]. Besides, glucocorticoids induce an upregulation of the enzyme phosphoenolpyruvate carboxykinase (PEPCK) activity in the liver, while simultaneously downregulating PEPCK activity in adipose tissue. Circulating free fatty acids increase, which leads to insulin resistance and gluconeogenesis.

While the effects of glucocorticoids widely differ based on patients who use them, even in healthy individuals, they may have a significant impact on metabolism, in animal models[89], and even in healthy people[90]. In a study which focused on metabolomic profiling in 20 healthy men, 214 plasmatic metabolites were analyzed before and after the administration of dexamethasone 4 mg. Overall, 150 of 214 metabolites were significantly altered even after a single dose of dexamethasone. All main energy pathways, including glycolysis, Krebs cycle, urea cycle and lipids, fatty acids and amino acids were altered with an expected inter-individual variability.
Given that glucocorticoids may have that much of an impact even in healthy individuals, patients more at risk of developing diabetes such as elderly patients, overweight or already insulin resistant patients may be even more impacted by the smallest dosages of glucocorticoids. In addition to usual risk factors of developing diabetes, other comorbidities are at risk of developing subsequent steroid-induced diabetes. Specifically, rheumatic disorders and patients afflicted with chronic kidney disease, treated by glucocorticoids may be at higher risk. In a retrospective study which included 128 non-diabetic patients with either rheumatic or renal disease who started glucocorticoids, 84 (65%) developed diabetes, much higher that the incidence observed in the overall population[91]. Independent variables associated with incidence of diabetes included age 65 years, HbA1c level 6% and glomerular filtration rate below 40 mL/min/1.73m². Interestingly, dosage did not influence risk of developing diabetes.

While dexamethasone treatment indicated during COVID-19 treatment is relatively short (10 d), adverse effects may occur. In-vitro, beta cell function was studied under three regimens of dexamethasone (0.1, 0.5, and 1.0 mg/kg) for 5 d. In the first group (0.1 mg/kg) beta cell function increased to satisfy insulin demand. In the second group (0.5 mg/kg), beta cell proliferation increased, associated with hyperinsulinemia but not hyperglycemia. Finally, the last group (1.0 mg/kg) presented hyperglycemia and hyperinsulinemia, and a major increase in beta-cell proliferation and size[92]. In-vivo, in 6 healthy men, a single-dose of 75 mg prednisolone did not change fasting plasma glucose or insulin, but decreased oral glucose insulin sensitivity[93]. On day 2 beta cells recovered, as evidenced by an increase in fasting insulin secretion. The same study also looked at the impact of a 2-wk exposure of prednisolone in 33 healthy men, the treatment increased the fasting plasma glucose, decreased the index of insulin resistance, and decreased the index of insulin sensitivity. These elements showed that prednisolone impairs beta cell function in healthy subjects, both in acute and 2-wk exposure, meaning that steroids induce insulin resistance but also beta cell dysfunction, even for these short periods of administration.

Interestingly, in RECOVERY trial, only few severe adverse events related to dexamethasone administration were reported, yet, among 4 severe adverse events reported, 2 (50%) included severe hyperglycemia[83]. Only time will allow to assess the incidence of diabetes in patients treated with dexamethasone, as compared to control treatment. Moreover, the influence of COVID-19 itself on the risk of developing diabetes needs to be accounted for.

## COVID-19 AS A RISK FACTOR OF DIABETES

### SARS-CoV-2 and diabetes

Infections, including COVID-19, may induce hyperglycemia in people without a previous diagnosis of diabetes. In fact, patients may present with stress hyperglycemia and thus, surpass the threshold only in the context of SARS-CoV-2 infection. Thus, hyperglycemia per se is not specific to COVID-19, especially since acute diabetes was commonly observed during SARS-CoV-1 epidemic among patients without prior history of diabetes and before the use of glucocorticoids[37]. However, the question has been raised as to whether SARS-CoV-2 can cause diabetes since new diabetes onset have been reported in numerous case reports simultaneously with acute SARS-CoV-2 infection. Although a meta-analysis of 8 studies including more than 3700 patients hospitalized for COVID-19 revealed a pooled incidence of 14.4% for new onset diabetes[94], mechanisms by which SARS-CoV-2 may induce diabetes remain unclear. Traditionally, 2 components are known to feature in diabetes pathogenesis: (1) Insulin resistance in the key tissues involved in glucose homeostasis, i.e., liver, skeletal muscles, and adipose tissue; and (2) Impaired insulin secretion by pancreatic β-cells.

### SARS-CoV-2 and ACE2

Structural evidence reported that ACE2 was the receptor of SARS-CoV-2. Viral infection of host cells occurs through viral spike protein and ACE2 receptor. SARS-CoV-2 entrance into host cells then induces ACE2 internalization and shedding, leading to a down-regulation of ACE2.

Of note, ACE2 belongs to the renin-angiotensin system (RAS). Briefly, angiotensinogen, produced by the liver, is cleaved by renin to form angiotensin-I which is then catalyzed by ACE to produce angiotensin-II (Ang II). ACE2 is a homologue of ACE that can hydrolyze Ang II to Ang-(1-7), whose reported effects include vasodilatation, anti-fibrosis, and anti-inflammation (these elements are
summarized in Figure 1). As Ang II is associated with insulin resistance[95], a major component of T2DM, disturbance of ACE2 activity by SARS-CoV-2 in glucose homeostasis key-tissues may induce acute hyperglycemia. In addition, ACE2 expression was also reported in the endocrine pancreas suggesting that SARS-CoV-2 may cause beta cell damage inducing diabetes through insulin secretion deficiency [96], but also in exocrine pancreatic cells[97]. Therefore, dysregulation of ACE2 activity caused by COVID-19 infection could lead to diabetes through several mechanisms.

SARS-CoV-2/ACE2 and insulin resistance-induced diabetes

One of the most obvious mechanisms by which SARS-CoV-2 induces insulin resistance is through systemic inflammation. Indeed, any inflammatory state can cause an insulin resistance leading to an increase hepatic glucose production through increased counter-regulatory hormones, cytokine and lipid release, and direct hepatocyte injury, irrespective of specific potential effects of SARS-CoV-2 on ACE2 activity and its repercussions on glucose homeostasis.

Then, since ACE2 is expressed in liver, skeletal muscles and adipose tissue, a disturbance in ACE2/Ang-(1-7) activity could lead to a glucose homeostasis disorder. Further support to this hypothesis comes from the fact that SARS-CoV-2 viral particles were not only identified in the cytoplasm of hepatocytes inducing a massive hepatic apoptosis[98], but were also involved in myositis occurrence[99]. Moreover, the loss of ACE2 gene in mice leads to hepatic fibrosis and impaired glucose homeostasis through an elevated hepatic reactive oxygen species level, an increased oxidative stress and inflammation in liver leading to an impairment of insulin signaling[100]. In adipose tissue, ACE2 deficiency worsens inflammation in response to a diet-induced obesity in mice[101]. Conversely, overexpression of ACE2 or Ang-(1-7) administration improves these metabolic disorders i.e., glycemic control and insulin sensitivity[102-104]. Indeed, mechanistically, Ang-(1-7) rescues insulin signaling pathway by stimulating PKB phosphorylation, a main mediator of insulin signaling pathway, what will then activate the downstream glycogen synthase kinase-3β in liver and skeletal muscles resulting in a decrease of glycaemia through glycogen storage[105], in several murine models of diet-induced insulin resistance such as high-fat diet fed mice or in fructose-fed rats[106,107]. In adipose tissue, activation of ACE2/Ang-(1-7) prevents inflammation and oxidative stress induced by a high-fat diet and increases glucose uptake and adiponectin level[108-110], while its disturbance results in a lower insulin-dependent glucose uptake and adiponectin secretion[111].

Besides the effects of the inhibition of the above mentioned alternate effects of the RAS, in the context of metabolic diseases such as obesity, T2DM or nonalcoholic fatty liver disease, plasmatic Ang II is positively correlated with body weight and is associated with insulin resistance, suggesting that ACE/Ang II activity is upregulated in those metabolic disorders[95]. Besides, on a tissue scale, Ang II was associated with increased insulin resistance through oxidative stress leading to a hepatic fibrosis and cirrhosis, provoking an impairment of insulin signaling[112]. In skeletal muscles, Ang II also induces a decreased glucose uptake and impairs insulin sensitivity[113], while in adipose tissue, it inhibits adiponectin secretion and insulin signaling still through an increased oxidative stress[114]. These elements emphasize the pro-diabetogenic effects of the classical RAS effects.

SARS-CoV-2/ACE2 and insulin secretion deficiency-induced diabetes

In a few COVID-19 human pancreas postmortem examinations, SARS-CoV-2 nucleocapsid protein were detected in pancreatic exocrine cells as well as in endocrine β-cells[115]. Furthermore, the RAS, including ACE2 was also found involved in the pancreatic insulin-producing tissue[116]. However, ACE2 expression by β cells responsible for insulin secretion remains controversial. Indeed, analyses from transcriptional datasets of human islet cells find a very weak expression of ACE2 in beta cells. These analyses are supported by immunohistochemistry of human pancreatic tissues that do not identify ACE2 expression on β cells but rather on ducts and microvascular structures[97], whereas double immunofluorescence labelling in rat pancreas indicates that insulin-containing beta cells abundantly express ACE2[117]. The latter observations suggest that ACE2 would play a role in insulin-containing beta cells and are supported by experiments in ACE2-deficient mice indicating that ACE2 loss aggravates beta cell dedifferentiation and impairs their proliferation, leading to a significant reduction of beta cell mass[118]. Similarly, in a genetic murine model of obesity and diabetes, ACE2 overexpression in pancreas, improved glycemic control through Ang-(1-7), inducing both β-cell proliferation and apoptosis reduction[102]. As expected, similarly as a loss of ACE2, Ang II supplementation in beta cells significantly increased endoplasmic reticulum (ER) stress and inflammation leading to reduced
Figure 1 Renin-angiotensin system: Classical and counter regulatory pathways. ACE: Angiotensin converting enzyme; ACE2: Angiotensin converting enzyme type 2; ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin-2 receptor 1 blockers; AT1R: Angiotensin II receptor type 1; AT2R: Angiotensin II receptor type 2; RAS: Renin-angiotensin system. Figure redrawn with permission from the authors (D. Laghlam et al.).

insulin secretion whereas Ang II receptor blockade in beta cells reduced significantly ER stress and rescues insulin secretion[119].

Moreover, ACE2 was also found on ductal structures and microvasculature of the pancreas, new diabetes onset may be secondary to pancreatitis as SARS-CoV-2 has been isolated in a pancreatic pseudocyst from a patient with acute pancreatitis. However, acute pancreatitis seems to be a very infrequent complication of SARS-CoV-2 infection. Two cohort studies which included 11000 and 63822 patients with COVID-19 respectively, acute pancreatitis prevalence was estimated at 0.27% and 0.07%[120]. Therefore, acute pancreatitis occurrence in patients with COVID-19 is exceedingly rare and its putative mechanism related to direct viral damage of pancreatic cells still need investigations.

Therefore, these findings suggest that ACE2 may play a role in the beta cell insulin secretory response to hyperglycemia and imply that SARS-CoV-2 could penetrate then destroy the insulin-containing beta cells, causing subsequently acute diabetes through insulin secretion deficiency.

SARS-CoV-2 and autoimmune type 1 diabetes

Viral infections, in particular by enteroviruses and coronaviruses, have been widely associated with T1DM pathogenesis[121]. T1DM is characterized by an autoimmune pancreatic β-cells progressive destruction leading to insulin deficiency. Therefore, SARS-CoV-2 could also act as an infectious trigger decompensating and precipitating diabetic ketoacidosis in patients with no history of diabetes as reported in few case reports[122-124], and arising evidence highlight the ability of SARS-CoV-2 to trigger autoimmune disorders[125]. Nonetheless, data remain conflictual on this point. Evidence from an Italian cross-sectional study revealed 23% fewer new-onset cases, with more children with new-onset disease presenting in diabetic ketoacidosis during early months of pandemic compared to the same period in 2019 while a multicenter study from the United Kingdom described an 80% increase in new-onset T1DM in children[126]. From a German Diabetes-Prospective Follow-up registry, the rate of new-onset T1DM from March to May 2020 did not differ significantly from rates observed over the previous decade[127]. However, when this study was done, COVID-19 infection incidence rate was relatively low in Germany, and weak effect cannot be excluded. Thus, from these studies, no compelling evidence emerge for a causal role of SARS-CoV-2 in a change of T1DM incidence. Furthermore, it was difficult to differentiate a viral secondary diabetes from a real T1DM as no assay for type 1 diabetes antibodies (GAD, IA2, ZNT8, ICA antibodies) has been performed in those series. More complexly, a few cases of insulin-dependent diabetes with negative antibodies start to emerge suggesting a T1bDM[128]. However, such form of diabetes is particularly widespread among Sub-Saharan African, African-Americans and Hispanic descendants and case reports concern Caucasian and Asian ethnicities suggesting a viral secondary diabetes more than a T1DM or T1bDM. Follow-up
studies on the evolution of anti-diabetic therapy are needed to understand the pathophysiology of SARS-CoV-2-induced diabetes.

In the end, the potential diabetogenic role of SARS-CoV-2 may be more complex than the simple beta cell hosts destruction by the virus through ACE2 expression. New-onset diabetes can result from several pathogenic processes involving pancreatic tissue through disturbance of ACE2/Ang-(1-7) activity.

CONCLUSION

Diabetic patients are heavily impacted by the effects of COVID-19, as they are more at risk of developing severe forms and are more at risk of mortality. While antidiabetic treatments are still under investigation, data do not warrant discontinuation of these treatments in diabetic patients. While corticosteroids count among the few validated treatments, they expose patients to a hypothetical risk of developing severe forms and are more at risk of mortality. While antidiabetic medications in severe COVID-19 pneumonia, they expose patients to a hypothetical risk of new onset of diabetes or diabetes deterioration, even though treatment duration is short. Finally, risk of developing diabetes after COVID-19, due to interactions with the angiotensin-converting-enzyme 2 needs to be accounted for when assessing risk of subsequent diabetes in treated patients.

REFERENCES

1. 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: 867-869 [PMID: 3222956 DOI: 10.1007/s40618-020-01236-2]

2. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA 2020; 323: 1775-1776 [PMID: 32203977 DOI: 10.1001/jama.2020.4683]

3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

4. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020; 180: 934-943 [PMID: 32167524 DOI: 10.1001/jamanetworkmed.2020.0994]

5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

6. Zhu L, She ZQ, Cheng X, Qin JJ, Zhang XJ, Cai J, Lei F, Wang H, Xie J, Wang W, Li H, Zhang P, Song X, Chen X, Xiang M, Zhang C, Bai L, Xiang D, Chen MM, Liu Y, Yan Y, Liu M, Mao W, Zou J, Liu L, Chen G, Luo P, Xiao B, Zhang Z, Lu Z, Wang J, Lu H, Xia X, Wang D, Liao X, Peng G, Ye P, Yang J, Yuan Y, Huang X, Guo J, Zhang BH. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab 2020; 31: 1068-1077.e3 [PMID: 32369736 DOI: 10.1016/j.cmet.2020.04.021]

7. McGurnaghan SJ, Weir A, Bishop J, Kennedy S, Blackbourn LAK, McAllister DA, Hutchinson S, Caparrotta TM, Mellor J, Jeyam A, O’Reilly JE, Wild SH, Hatam S, Höhn A, Colombo M, Robertson C, Lone N, Murray J, Petty J, Pets J, Petrie J, Kennedy S, Blackbourn LAK, McAllister DA, Hutchinson S, Caparrotta TM, Mellor J, Jeyam A, O’Reilly JE, Wild SH, Hatam S, Höhn A, Colombo M, Robertson C, Lone N, Murray J, Petty J, Pets J, Petrie J, and the Scottish Diabetes Research Network Epidemiology Group. Risks of and risk factors for COVID-19 in people with diabetes: a cohort study of the total population of Scotland. Lancet Diabetes Endocrinol 2021; 9: 82-93 [PMID: 33337491 DOI: 10.1016/S2213-8587(20)30405-8]

8. Wargny M, Potier L, Gourdy P, Pichelin M, Amadou C, Benhamou PY, Bonnet JB, Bordier L, Bourron O, Chaumeil C, Chevalier N, Darmon P, Delente B, Demarsy D, Dumas M, Dupuy O, Flaus-Furmaniak A, Gauthier JF, Guoed AM, Jeandidier N, Leger E, Le Berre JP, Lungo M, Montanier N, Moulin P, Plat F, Rigalleau V, Robert R, Seret-Bégue D, Sérusclat P, Smati S, Thébaut F, Trimunt B, Vatier C, Velayoudoum FL, Vergès B, Winiszewski P, Zabulon A, Gourraud PA, Roussel R, Cariou B, Hadjadj S; CORONADO investigators. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. Diabetologia 2021; 64: 778-794 [PMID: 33599800 DOI: 10.1007/s00125-020-05351-w]
Sabri S et al. Diabetes and COVID-19

9 Agarwal S, Schechter C, Southern W, Crandall JP, Tomer Y. Preadmission Diabetes-Specific Risk Factors for Mortality in Hospitalized Patients With Diabetes and Coronavirus Disease 2019. *Diabetes Care* 2020; 43: 2339-2344 [PMID: 32769128 DOI: 10.2337/dc20-1543]

10 Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJ, Ballie JK, Semple MG; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020; 369: m1985 [PMID: 32444460 DOI: 10.1136/bmj.m1985]

11 Mantovani A, Byrne CD, Zheng MH, Targar G. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis* 2020; 30: 1236-1248 [PMID: 32571616 DOI: 10.1016/j.numecd.2020.05.014]

12 Istituto Superiore di Sanità. Report of characteristics of patients died positive for COVID-19 in Italy. [cited 20 May 2021]. Available from: https://www.epicentro.iss

13 Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Domineflo AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; 323: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]

14 National Health Interview Survey. Early release of selected estimates based on data from the 2019 National Health Interview Survey. [cited 20 May 2021]. Available from: https://www.cdc.gov/nchs/nhis/releases/released201905.htm

15 Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion TR Jr, Nahid M, Ringel JB, Hoffman KL, Aishak MN, Li HA, Wehmeyer GT, Rajan M, Reshetyuk E, Hupert N, Horn EM, Martinez FJ, Gulick RM, Saifod MM. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med* 2020; 382: 2372-2374 [PMID: 32302078 DOI: 10.1056/NEJMoa201419]

16 Petrilli CM, Jones SA, Yang J, Rajagopal H, O’Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020; 369: m1966 [PMID: 32444466 DOI: 10.1136/bmj.m1966]

17 Suleyman G, Fadel RA, Malette KM, Hammond C, Abdulla H, Entz A, Demertzis Z, Hanna Z, Faila A, Dagher C, Chaudhry Z, Vahia A, Abreu Lanfranco O, Ramesh M, Zervos MJ, Alangaden GS, Suleyman G, Miller J, Brar I. Clinical Characteristics and Morbidity Associated With Coronavirus Disease 2019 in a Series of Patients in Metropolitan Detroit. *JAMA Netw Open* 2020; 3: e2012270 [PMID: 32543702 DOI: 10.1001/jamanetworkopen.2020.12270]

18 Shi Q, Zhang X, Jiang F, Hu N, Bimu C, Feng J, Yan S, Guan Y, Xu D, He G, Chen C, Xiong X, Liu L, Li H, Tao J, Peng Z, Wang W. 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: 1382-1391 [PMID: 32409504 DOI: 10.2337/dc20-0598]

19 Schlesinger S, Neuenschwander M, Lang A, Papili K, Kuss O, Herder C, Roden M. Risk phenotypes of diabetes and association with COVID-19 severity and death: a living systematic review and meta-analysis. *Diabetologia* 2021; 64: 1480-1491 [PMID: 33907860 DOI: 10.1007/s00125-021-05458-8]

20 Vangeuillezheven R, Martens PJ, van Nes F, Moyson C, Nobels F, Van Crombrugghe P, Wierckx K, van Pottelbergh I, Van Hulstel F, Gillard P, Mathieu C. No Evidence of Increased Hospitalization Rate for COVID-19 in Community-Dwelling Patients With Type 1 Diabetes. *Diabetes Care* 2020; 43: e118-e119 [PMID: 32647055 DOI: 10.2337/dc20-1246]

21 Holman N, Knighton P, Kar P, O’Keefe J, Curley M, Weaver A, Barron E, Bakshi C, Khunti K, Wareham NJ, Sattar N, Young B, Valabhji J. 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; 8: 823-833 [PMID: 32798471 DOI: 10.1016/S2213-8587(20)30271-0]

22 Barron E, Bakshi C, Kar P, Weaver A, Bradley D, Ismaiil H, Knighton P, Holman N, Khunti K, Sattar N, Wareham NJ, Young B, Valabhji J. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020; 8: 813-822 [PMID: 32798472 DOI: 10.1016/S2213-8587(20)30272-2]

23 d’Annuozio G, Maffeis C, Cherubini V, Rabbone I, Scaramuzza A, Schiaffini R, Minuto N, Piccolo G, Maghnie M. Caring for children and adolescents with type 1 diabetes mellitus: Italian Society for Pediatric Endocrinology and Diabetology (ISPED) statements during COVID-19 pandemic. *Diabetes Res Clin Pract* 2020; 168: 108372 [PMID: 32827596 DOI: 10.1016/j.diabres.2020.108372]

24 Verma A, Rajput R, Verma S, Balania VKB, Jangra B. Impact of lockdown in COVID 19 on glycemic control in patients with type 1 Diabetes Mellitus. *Diabetes Metab Syndr* 2020; 14: 1213-1216 [PMID: 32679527 DOI: 10.1016/j.dsx.2020.07.016]

25 Caussy C, Pattou F, Wallet F, Simon C, Chalopin S, Telliam C, Mathieu D, Subtil F, Frobert E, Alligier M, Delaunay D, Vanhems P, Laville M, Jourdain M, Disse E; COVID Outcomes HCL Consortium and Lille COVID–Obesity Study Group. Prevalence of obesity among adult inpatients with COVID-19 in France. *Lancet Diabetes Endocrinol* 2020; 8: 562-564 [PMID: 32437642 DOI: 10.1016/S2213-8587(20)30160-1]

26 Gao M, Piernas C, Astbury NM, Hippius-Cox J, O’Rahilly S, Aveyard P, Jebb SA. Associations
between body-mass index and COVID-19 severity in 6.9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol 2021; 9: 350-359 [PMID: 33932335 DOI: 10.1016/S2213-8587(21)00089-9]

27 Smati S, Tramunt B, Wargny M, Causse Y, Gaborit B, Vautier C, Vergès B, Ancelle D, Amadou C, Bachir LA, Bourroul O, Coffin-Boutreux C, Barraud S, Dorange A, Freny B, Gaultier JF, Germain N, Larger E, Laugier-Robiolle S, Meyer L, Monier A, Moura I, Potier L, Sabah N, Soret-Bégué D, Winiszewski P, Pichelin M, Saulnier PJ, Hadjadj S, Curcio B, van der Poll T, CORONADO investigators. Relationship between obesity and severe COVID-19 outcomes in patients with type 2 diabetes: Results from the CORONADO study. Diabetes Obes Metab 2021; 23: 391-403 [PMID: 33051976 DOI: 10.1111/dom.14228]

28 Sardu C, D’Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, Maggi P, Coppola N, Paolisso G, Marfella R. Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? Diabetes Care 2020; 43: 1408-1415 [PMID: 32430456 DOI: 10.2337/dc20-0723]

29 Chao WC, Tseng CH, Wu CL, Shih SJ, Yi CY, Chan MC. Higher glycemic variability within the first day of ICU admission is associated with increased 30-day mortality in ICU patients with sepsis. Ann Intensive Care 2020; 10: 17 [PMID: 32034567 DOI: 10.1186/s13613-020-00635-3]

30 Shen Y, Fan X, Zhang L, Wang Y, Li C, Lu J, Zha B, Wu Y, Chen X, Zhou J, Jia W. Thresholds of Glycemia and the Outcomes of COVID-19 Complicated With Diabetes: A Retrospective Exploratory Study Using Continuous Glucose Monitoring. Diabetes Care 2021; 44: 976-982 [PMID: 33574126 DOI: 10.2337/dc20-1448]

31 Lepper PM, Ott S, Niessch E, von Eynatten M, Schumann C, Plettz MW, Mealing NM, Welte T, Bauer TT, Suttorp N, Jinji P, Bals R, Rohde G. German Community Acquired Pneumonia Competence Network. Serum glucose levels for predicting death in patients admitted to hospital for community acquired pneumonia: prospective cohort study. BMJ 2012; 344: e3397 [PMID: 22645184 DOI: 10.1136/bmj.e3397]

32 Lepper PM, Bals R, Jinji P, von Eynatten M. Blood glucose, diabetes and metabolic control in patients with community-acquired pneumonia. Diabetologia 2020; 63: 2488-2490 [PMID: 32667817 DOI: 10.1007/s00125-020-02525-1]

33 Benfield T, Jensen JS, Nordestgaard BG. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. Diabetologia 2007; 50: 549-554 [PMID: 17187246 DOI: 10.1007/s00125-006-0570-3]

34 Harding JL, Benoit SR, Gregg EW, Pavkov ME, Perreault L. Trends in Rates of Infections Requiring Hospitalization Among Adults With Versus Without Diabetes in the U.S., 2000-2015. Diabetes Care 2020; 43: 106-116 [PMID: 31615853 DOI: 10.2337/dc19-0653]

35 Magliano DJ, Harding JL, Cohen K, Huxley RR, Davis WA, Shaw JE. Excess Risk of Dying From Infectious Causes In Those With Type 1 and Type 2 Diabetes. Diabetes Care 2015; 38: 1274-1280 [PMID: 26070592 DOI: 10.2337/dc14-2820]

36 Alqahtani FY, Aleantzis FS, Ali El Hadi Mohamed R, Alanazi MS, Mohamed N, Alrasheed MM, Abanmy N, Alhawass T. Prevalence of comorbidities in cases of Middle East respiratory syndrome coronavirus: a retrospective study. Epidemiol Infect 2018; 147: e35 [PMID: 30394248 DOI: 10.1017/S0950268818002923]

37 Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JC. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006; 23: 623-628 [PMID: 16579303 DOI: 10.1111/j.1479-5876.2006.01861.x]

38 Stegenga ME, van der Crabben SN, Blümer RM, Levi M, Meijers JC, Serlie MJ, Tanck MW, Sauerwein HP, van der Poll T. Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. Blood 2008; 112: 82-89 [PMID: 18316629 DOI: 10.1182/blood-2007-11-121725]

39 Delamare M, Maugendre D, Moreno M, Goff MC, Allamnic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabet Med 1997; 14: 29-34 [PMID: 9017350 DOI: 10.1002/sdi.4280140107]

40 Critchley AA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. Diabetes Care 2018; 41: 2127-2135 [PMID: 30104296 DOI: 10.2337/dc18-0287]

41 Hair PS, Echague CG, Rohn RD, Krishna NK, Nyalwidhe JO, Cunnion KM. Hyperglycemic conditions inhibit C3-mediated immunologic control of Staphylococcus aureus. J Transl Med 2012; 10: 35 [PMID: 22390383 DOI: 10.1186/1479-5876-10-35]

42 Stegenga ME, van der Crabben SN, Dessing MC, Pater JM, van den Pangaart PS, de Vos AF, Tanck MW, Roos D, Sauerwein HP, van der Poll T. Effect of acute hyperglycaemia and/or hyperinsulinaemia on proinflammatory gene expression, cytokine production and neutrophil function in humans. Diabet Med 2008; 25: 157-164 [PMID: 18290856 DOI: 10.1111/j.1464-5491.2007.02348.x]

43 Codo AC, Davanzo GG, Monteiro LB, de Souza GF, Murapo SP, Virgilio-da-Silva JV, Prodonoff JS, Carregaci VC, de Biagi Junior CAO, Cruufli F, Jimenez Restrepo JL, Vendramini PH, Reis-de-Oliveira G, Bispo Dos Santos K, Toledo-Teixeira DA, Parise PL, Marini MC, Marques RE, Carmo HR, Borin A, Coimbra LD, Boldrini VO, Brunetti NS, Vieira AS, Mansour E, Ulaf RG, Bernardes AF, Nunes TA, Ribeiro LC, Palma AC, Agrela MV, Moretti ML, Sposito AC, Pereira FB, Velloso
Sabri S et al. Diabetes and COVID-19

LA, Vinolo MAR, Damasio A, Proença-Môdena JL, Carvalho RF, Mori MA, Martins-de-Souza D, Nakaya HI, Farias AS, Moraes-Vieira PM. Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1α/Glycolysis-Dependent Axis. Cell Metab 2020; 32: 437-446.e5 [PMID: 32697943 DOI: 10.1016/j.cmet.2020.07.007]

Lampanosa V, Secchi M, Scavini M, Bazzigaluppi E, Brigatti G, Marzinotto I, Davalli A, Carento A, Laurenzi A, Martinenghi S, Molinari C, Vitali G, Di Filippo L, Mercalli A, Melzi R, Tresoldi C, Rovere-Quarrini P, Landoni G, Cicci F, Bosi E, Pemonti L. Antibody response to multiple antigens of SARS-CoV-2 in patients with diabetes: an observational cohort study. Diabetologia 2020; 63: 2548-2558 [PMID: 33092657 DOI: 10.1007/s00125-020-05284-4]

Ektunde AO, Mellacharuvu SP, Ooreoluwa P. A Review of Postmortem Findings in Patients With COVID-19. Curesus 2020; 12: e9438 [PMID: 32864262 DOI: 10.7759/curesus.9438]

Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, Yu X, Dong K. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Res Care 2020; 8 [PMID: 32345579 DOI: 10.1136/bmjdrd-2020-001343]

Alzaid F, Julla JB, Diedischm M, Potier C, Potier L, Velho G, Gaborit P, Manivet P, Germain S, Vidal-Trecan T, Roussei R, Riveline JP, Dalmas E, VenteclFN, Gautier JF. Monocytopenia, monocyte morphologic anomalies and hyperinflammation characterise severe COVID-19 in type 2 diabetes. EMBO Mol Med 2020; 12: e13038 [PMID: 32816392 DOI: 10.15222/emmm.202103038]

Murugan AT, Sharma G. Obesity and respiratory diseases. Chron Respir Dis 2008; 5: 233-242 [DOI: 10.1029/2008CR001775]

Schubert L, Larocco S, Hartemann A, Bourron O, Phan F. Impaired hypoxia ventilatory drive induced by diabetic autonomic neuropathy, a cause of misdiagnosed severe cardiac events: brief report of two cases. BMC Cardiovasc Disord 2021; 21: 140 [PMID: 33731006 DOI: 10.1186/s12872-021-01944-4]

Zhou YJ, Zheng KJ, Wang XB, Sun QF, Pan KH, Wang TY, Ma HL, Chen YP, George J, Zheng MH. Metabolic-associated fatty liver disease is associated with severity of COVID-19. Liver Int 2020; 40: 2160-2163 [PMID: 32573883 DOI: 10.1111/liv.14575]

Ren H, Yang Y, Wang F, Yan Y, Shi X, Dong K, Yu X, Zhang S. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. Cardiovasc Diabetol 2020; 19: 58 [PMID: 32393351 DOI: 10.1186/s12933-020-01035-2]

De Bandt JP, Monin C. Obesity, Nutrients and the Immune System in the Era of COVID-19. Nutrients 2021; 13 [PMID: 33668493 DOI: 10.3390/nu13020610]

Zhang AJ, To KK, Li C, Lau CC, Poon VK, Chan CC, Zheng BJ, Hung IF, Lam KS, Xu A, Yuen KY. Leptin mediates the pathogenesis of severe 2019 pandemic influenza A(H1N1) infection associated with cytokine dysregulation in mice with diet-induced obesity. J Infect Dis 2013; 207: 1270-1280 [PMID: 23232916 DOI: 10.1093/infdis/jit031]

Karampela I, Christodoulatos OS, Dalamaga M. The Role of Adipose Tissue and Adipokines in Sepsis: Inflammatory and Metabolic Considerations, and the Obesity Paradox. Curr Obes Rep 2019; 8: 434-457 [PMID: 31637623 DOI: 10.1007/s13679-019-00360-2]

Ryan PM, Caplice NM. Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation, and Cytokine Amplification in Coronavirus Disease 2019? Obesity (Silver Spring) 2020; 28: 1191-1194 [PMID: 32314868 DOI: 10.1002/oby.22843]

Argyropoulos KY, Serrano A, Hu J, Black M, Feng X, Shen G, Call M, Kim MJ, Lytle A, Belovarac B, Vougoukklakis T, Lin LH, Moran U, Heguy A, Troxel A, Snuderl M, Osman I, Cotzia P, Jour G. Association of Initial Viral Load in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Patients with Outcome and Symptoms. Am J Pathol 2020; 190: 1881-1887 [PMID: 32628931 DOI: 10.1016/j.ajpath.2020.07.001]

Chung WS, Lin CL, Kao CH. Diabetes increases the risk of deep-vein thrombosis and pulmonary embolism. A population-based cohort study. Thromb Haemost 2015; 114: 812-818 [PMID: 26271946 DOI: 10.1160/TH14-10-0868]

Poissy J, Goutay J, Caplan M, Parmentier E, Duburq T, Lassalle F, Jeanpierre E, Rauch A, Labeurche J, Susen S; Lille ICU Haemostasis COVID-19 Group. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. Circulation 2020; 142: 184-186 [PMID: 32330083 DOI: 10.1161/CIRCULATIONAHA.120.047430]

Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Shehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehr MA, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. Nat Med 2020; 26: 1017-1032 [PMID: 32651579 DOI: 10.1038/s41591-020-0968-3]

Oxford AE, Halla F, Robertson EB, Morrison BE. Endothelial Cell Contributions to COVID-19. Pathogens 2020; 9 [PMID: 32992810 DOI: 10.3390/pathogens9100785]

De Vriese AS, Verbueren TJ, Van de Voorde J, Lameire NH, Vanhoutte PM. Endothelial dysfunction in diabetes. Br J Pharmacol 2000; 130: 963-974 [PMID: 10882379 DOI: 10.1038/sj.bjp.0703393]

Khunti K, Knighton P, Zaccardi F, Bakhai C, Barron E, Holman N, Kar P, Meace C, Sattar N, Sharp S, Wareham NJ, Weaver A, Woch E, Young B, Valabhj J. Prescription of glucose-lowering
therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. *Lancet Diabetes Endocrinol* 2021; 9: 293-303 [PMID: 33798464 DOI: 10.1016/S2213-8587(21)00500-4]

64 **Mirani M**, Favacchio G, Carrone F, Betella N, Biamonte E, Morenghi E, Mazzotti G, Lania AG. Impact of Comorbidities and Glycemia at Admission and Dipeptidyl Peptidase 4 Inhibitors in Patients With Type 2 Diabetes With COVID-19: A Case Series From an Academic Hospital in Lombardy, Italy. *Diabetes Care* 2020; 43: 3042-3049 [PMID: 33023980 DOI: 10.2337/dc20-1340]

65 **Gorricho J**, Garón J, Alonso A, Celaya MC, Saiz LC, Erviti J, López A. Use of oral antidiabetic agents and risk of community-acquired pneumonia: a nested case-control study. *Br J Clin Pharmacol* 2017; 83: 2034-2044 [PMID: 28294379 DOI: 10.1111/bcp.13288]

66 **Li Y**, Zhang Z, Yang L, Liu X, Xie Y, Li S, Xin S, Cao P, Lu J. The MERS-CoV Receptor DPP4 as a Candidate Binding Target of the SARS-CoV-2 Spike. *Science* 2020; 23: 101160 [PMID: 32405622 DOI: 10.1111/jisci.2020.101160]

67 **Vankadari N**, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glucan shield and structure prediction of spike glycoprotein and its interaction with human CD26. *Emerg Microbes Infect* 2020; 9: 601-604 [PMID: 32178593 DOI: 10.1080/22227517.2020.1739565]

68 **Roussel R**, Darmon P, Pichelin M, Goronflot T, Aboueleka Y, Ait Bachir L, Allix I, Ancelle D, Barraud S, Bordier L, Carlier A, Chevalier N, Coffin-Bouteux C, Cosson E, Dorange A, Dupuy O, Fontaine P, Fremy B, Galtier F, Germain N, Guedj AM, Leger E, Lauzier-Roholle S, Laviolle B, Ludwig L, Monier A, Montanier N, Moulin P, Moura I, Prevost G, Reznik Y, Sahl S, Saulnier PJ, Seluschat P, Vatier C, Wargny M, Hadjadj S, Gourdy P, Cariou B; CORONADO investigators. Use of dipeptidyl peptidase-4 inhibitors and prediction of COVID-19 in hospitalized patients with type 2 diabetes: a propensity score analysis from the CORONADO study. *Diabetes Obes Metab* 2021; 23: 1162-1172 [PMID: 33528920 DOI: 10.1111/dom.14324]

69 **Scheen AJ**. Metformin and COVID-19: From cellular mechanisms to reduced mortality. *Diabetes Metab* 2020; 46: 423-426 [PMID: 32750541 DOI: 10.1016/j.diabet.2020.07.006]

70 **Han JH**, Oh TJ, Lee G, Maeng HJ, Lee DH, Kim KM, Choi SH, Jang HC, Lee HS, Park KS, Kim YB, Lim S. The beneficial effects of empagliflozin, an SGLT2 inhibitor, on atherosclerosis in ApoE -/- mice fed a western diet. *Diabetologia* 2017; 60: 364-376 [PMID: 27866224 DOI: 10.1007/s00125-016-4158-2]

71 **Garvey WT**, Van Gaal L, Leiter LA, Vijapurkar U, List J, Cuddihy R, Ren J, Davies MJ. Effects of canagliflozin versus glimepiride on adipokines and inflammatory biomarkers in type 2 diabetes. *Metabolism* 2018; 85: 32-37 [PMID: 29452178 DOI: 10.1016/j.metabol.2018.02.002]

72 **Kosiborod M**, Berwanger O, Koch GG, Martinez F, Mukhtar O, Verma S, Chopra V, Javaheri A, Ambrey P, Gasparyan SB, Buenconsejo J, Sjöström CD, Langkilde AM, Oscarsson J, Esterline R. Effects of dapagliflozin on prevention of major clinical events and recovery in patients with respiratory failure because of COVID-19: Design and rationale for the DARE-19 study. *Diabetes Obes Metab* 2021; 23: 886-896 [PMID: 33319454 DOI: 10.1111/dob.14290]

73 **Arakawa M**, Mitu T, Azuma K, Ebato C, Goto H, Nomiyama T, Fujitani Y, Hirose T, Kawamori R, Watanabe H. Inhibition of monocyte adhesion to endothelial cells and attenuation of atherosclerotic lesion by a glucagon-like peptide-1 receptor agonist, exendin-4. *Diabetes* 2010; 59: 1030-1037 [PMID: 20668138 DOI: 10.2337/db09-1694]

74 **Ceriello A**, Kilpatrick ES. Glycemic variability: both sides of the story. *Diabetes Care* 2013; 36 Suppl 2: S272-S275 [PMID: 23882058 DOI: 10.2337/dc13-S109]

75 **Vilny 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: 4503-4511 [PMID: 24092637 DOI: 10.1210/en.2013-1666]

76 **Dambha-Miller H**, Albasri A, Hodgson S, Wilcox CR, Khan S, Islam N, Little P, Griffin SJ. Currently prescribed drugs in the UK that could upregulate or downregulate ACE2 in COVID-19 disease: a systematic review. *BMJ Open* 2020; 10: e040644 [PMID: 32928868 DOI: 10.1136/bmjopen-2020-040644]

77 **Laalau JD**, Al-Salamah A, Hadjadji S, Goronflot T, Wiensperger N, Pichelin M, Allix I, Amadou C, Bourron O, Duriez T, Gautier JF, Dutout A, Gonnef C, Gouet D, Joubert M, Julier I, Leger E, Marchand L, Marre M, Meyer L, Olivier F, Prevost G, Quinou P, Raffaït-Cardin C, Roussel R, Saulnier PJ, Serret-Beque D, Thivolet C, Vatier C, Desailloud H, Wargny M, Gourdy P, Cariou B; CORONADO investigators. Metformin use is associated with a reduced risk of mortality in patients with diabetes hospitalised for COVID-19. *Diabetes Metab* 2020; 47: 101216 [PMID: 33309936 DOI: 10.1016/j.diabet.2020.101216]

78 **Cheng X**, Xin S, Chen Y, Li L, Chen W, Li W, Zhou B, Li C, Gong Y, Li F, Duan P, Zhou X. Effects of metformin, insulin on COVID-19 patients with pre-existent type 2 diabetes: A multicentric retrospective study. *Life Sci* 2021; 275: 119371 [PMID: 33745895 DOI: 10.1016/j.lfs.2021.119371]

79 **Wiensperger N**. Metformin as a cellular protector; a synoptic view of modern evidences. *J Nephropathol* 2015; 4: 31-36 [PMID: 28197472]

80 **Zangibadian M**, Nejadghaderi SA, Zahmatkesh MM, Hajikhani B, Mirsaedi M, Nasiri MJ. The Efficacy and Potential Mechanisms of Metformin in the Treatment of COVID-19 in the Diabetics: A Systematic Review. *Front Endocrinol (Lausanne)* 2021; 12: 645194 [PMID: 33815295 DOI: 10.3389/fendo.2021.645194]

81 **Bramante CT**, Ingraham NE, Murray TA, Marmor S, Hoversons S, Gronski J, McNeil C, Feng R,
Guzman G, Abdelwahab N, King S, Tamariz L, Meehan T, Pendleton KM, Benson B, Vojta D, Tiganelli CJ. Metformin and risk of mortality in patients hospitalised with COVID-19: a retrospective cohort analysis. *Lancet Healthy Longev* 2021; 2: e34-e41 [PMID: 33521772 DOI: 10.1016/S2666-7588(20)30033-7]

82 Liang H, Ding X, Li L, Wang T, Kan Q, Wang L, Sun T. Association of preadmission metformin use and mortality in patients with sepsis and diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Crit Care* 2019; 23: 50 [PMID: 30777119 DOI: 10.1186/s13054-019-2346-4]

83 RECOVERY Collaborative Group, Horby P, Lim WS, Emberson J, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmalı E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Bailleil JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; 384: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa201436]

84 WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O, Cavalcanti AB, Dequin PF, Du B, Emberson J, Fisher D, Giraudence B, Gordon AC, Granholm A, Green C, Haynes R, Heming N, Higgins JPT, Horby P, Jiuni P, Landray MJ, Le Gouge A, Leclerc M, Lim WS, Machado FR, McArthur C, Meziani F, Müller MH, Perner A, Petersen MW, Savovic J, Tomazini B, Veiga VC, Webb S, Marshall JC. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020; 324: 1330-1341 [PMID: 32876694 DOI: 10.1001/jama.2020.17023]

85 American Diabetes Association. 2. Classification and Diagnosis of Diabetes. *Diabetes Care* 2017; 40: S11-S24 [PMID: 27979889 DOI: 10.23736/diabetes.236.2020.02067.x]

86 Liang J, Weiss RE. Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. *Diabetes Metab Rev* 2014; 30: 96-102 [PMID: 24123849 DOI: 10.1002/dmrr.2486]

87 Liu X, Zhu XM, Miao Q, Ye HY, Zhang ZY, Li YM. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. *Ann Nutr Metab* 2014; 65: 324-332 [PMID: 25402408 DOI: 10.1159/000365892]

88 van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabeticogenic effects: towards expansion of therapeutic options? *Eur J Clin Invest* 2009; 39: 81-93 [PMID: 19200161 DOI: 10.1111/j.1365-2362.2008.02067.x]

89 Lambillotte C, Gilon P, Henquin JC. Direct glucocorticoid inhibition of insulin secretion. An in vitro study of dexamethasone effects in mouse islets. *J Clin Invest* 1997; 99: 414-423 [PMID: 9020748 DOI: 10.1172/JCI19175]

90 Bordag N, Klie S, Jürchott K, Schiewe H, Albrecht V, Tonn JC, Schwartz C, Schichor K, Seibj J. Glucocorticoid (dexamethasone)-induced metabolome changes in healthy males suggest prediction of response and side effects. *Sci Rep* 2015; 5: 15954 [PMID: 26526738 DOI: 10.1038/srep15954]

91 Katsuyama T, Sada KE, Namba S, Watanabe H, Katsuyama E, Yamanari T, Wada I, Makino H. Risk factors for the development of glucocorticoid-induced diabetes mellitus. *Diabetes Res Clin Pract* 2015; 108: 273-279 [PMID: 25765669 DOI: 10.1016/j.diabres.2015.02.010]

92 Rafacho A, Cestari TM, Taboga SR, Boscherio AC, Bosqueiro JR. High doses of dexamethasone induce increased beta-cell proliferation in pancreatic rat islets. *Am J Physiol Endocrinol Metab* 2009; 296: E681-E689 [PMID: 19158320 DOI: 10.1152/ajpendo.09031.2008]

93 van Raalte DH, Nofrite V, Bunck MC, van Iersel T, Elassaiss Schaap J, Nässander UK, Heine RJ, Mari A, Dokter WH, Diamant M. Acute and 2-week exposure to prednisolone impair different aspects of beta-cell function in healthy men. *Eur J Endocrinol* 2010; 162: 729-735 [PMID: 20124412 DOI: 10.1530/EJE-09-1034]

94 Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmert P. Proportion of newly diagnosed diabetes in COVID-19 patients: A systematic review and meta-analysis. *Diabetes Obes Metab* 2021; 23: 870-874 [PMID: 33245182 DOI: 10.1111/dom.14269]

95 Saiaki A, Ohira M, Endo K, Koide N, Oyama T, Murano T, Miyashita Y, Shirai K. Circulating angiotensin II is associated with body fat accumulation and insulin resistance in obese subjects with type 2 diabetes mellitus. *Metabolism* 2009; 58: 708-713 [PMID: 19375596 DOI: 10.1016/j.metabol.2009.01.013]

96 Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol* 2010; 47: 193-199 [PMID: 19333547 DOI: 10.1007/s00592-009-0109-4]

97 Coate KC, Cha J, Shrestha S, Wang W, Gonçalves LM, Almaça J, Kapp ME, Fasołino M, Morgan A, Dai C, Saunders DC, Bottino R, Aramandla R, Jenkins R, Stein R, Kaestner KH, Vahedi G; HPAP Consortium, Brissova M, Powers AC. SARS-CoV-2 Cell Entry Factors ACE2 and TMPRSS2 Are Expressed in the Microvasculature and Ducts of Human Pancreas but Are Not Enriched in β Cells. *Cell Metab* 2020; 32: 1028-1040.e4 [PMID: 33207245 DOI: 10.1016/j.cmet.2020.11.006]

98 Wang Y, Liu S, Liu H, Li W, Lin F, Jiang L, Li X, Xu P, Zhang L, Zhao L, Cao Y, Kang J, Yang J, Li L, Liu X, Li Y, Nie R, Mu J, Lu F, Zhao S, Lu J, Zhao J. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020; 73: 807-816 [PMID: 32437830 DOI: 10.1016/j.jhep.2020.05.002]

99 Beydon M, Chevalier K, Al Tabaa O, Hamroun S, Delette AS, Thomas M, Herrou J, Riviere E, Mariette X. Myositis as a manifestation of SARS-CoV-2. *Ann Rheum Dis* 2020; 79: 807-816 [PMID: 32437830 DOI: 10.1136/annrheumdis-2020-219567]
100 Niu MJ, Yang JK, Lin SS, Ji XJ, Guo LM. Loss of angiostatin-converting enzyme 2 leads to impaired glucose homeostasis in mice. Endocrine 2008; 34: 56-61 [PMID: 18956256 DOI: 10.1007/s12020-008-9110-x]

101 Montaigne D, Coisne A, Marechal X, Staels B. Comment on Patel et al. ACE2 Deficiency Worsens Epidermal Adipose Tissue Inflammation and Cardiac Dysfunction in Response to Diet-Induced Obesity. Diabetes 2016; 65: 85-95. Diabetes 2016; 65: e1-e2 [PMID: 26798127 DOI: 10.2337/db15-1425]

102 Bindom SM, Hans CP, Xia H, Boulares AH, Lazartigues E. Angiostatin I-converting enzyme type 2 (ACE2) gene therapy improves glycemic control in diabetic mice. Diabetes 2010; 59: 2540-2548 [PMID: 20660625 DOI: 10.2337/db09-0782]

103 Österreicher CH, Taura K, De Minicis S, Seki E, Penz-Osterreicher M, Kodama Y, Kluve J, Schuster M, Oudit GY, Penninger JM, Brenner DA. Angiostatin-converting enzyme 2 inhibits liver fibrosis in mice. Hepatology 2009; 50: 929-938 [PMID: 19650157 DOI: 10.1002/hep.23104]

104 Cao X, Yang F, Shi T, Yuan M, Xin Z, Xie R, Li S, Li H, Yang JK. Angiostatin-converting enzyme 2/angiostatin-(1-7)/Mas axis activates Akt signaling to ameliorate hepatic steatosis. Sci Rep 2016; 6: 21592 [PMID: 26883364 DOI: 10.1038/srep21592]

105 Muñoz MC, Giani JF, Dominici FP. Angiostatin-(1-7) stimulates the phosphorylation of Akt in rat extracardiac tissues in vivo via receptor Mas. Regul Pept 2010; 161: 1-7 [PMID: 20188769 DOI: 10.1016/j.regpep.2010.02.001]

106 Feltenberger JD, Andrade JM, Paraíso A, Barros LO, Filho AB, Sinisterra RD, Sousa FB, Guimarães AL, de Paula AM, Campagnole-Santos MJ, Qureshi M, dos Santos RA, Santos SH. Oral formulation of angiostatin-(1-7) improves lipid metabolism and prevents high-fat diet-induced hepatic steatosis and inflammation in mice. Hypertension 2013; 62: 324-330 [PMID: 23753417 DOI: 10.1161/HYPERTENSIONAHA.111.09919]

107 Santos SH, Andrade JM, Fernandes LR, Sinisterra RD, Sousa FB, Feltenberger JD, Alvarez-Leite JI, Santos RA. Oral Angiostatin-(1-7) prevented obesity and hepatic inflammation by inhibition of resistin/TLR4/MAPK/NAF-xB in rats fed with high-fat diet. Peptides 2013; 46: 47-52 [PMID: 23714175 DOI: 10.1016/j.peptides.2013.05.010]

108 Santos SH, Fernandes LR, Pereira CS, Guimarães AL, de Paula AM, Campagnole-Santos MJ, Alvarez-Leite JI, Bader M, Santos RA. Increased circulating angiostatin-(1-7) protects white adipose tissue against development of a proinflammatory state stimulated by a high-fat diet. Regul Pept 2012; 178: 64-70 [PMID: 22749992 DOI: 10.1016/j.regpep.2012.06.009]

109 Liu C, Lv XH, Li HX, Cao X, Zhang F, Wang L, Yu M, Yang JK. Angiostatin-(1-7) suppresses oxidative stress and improves glucose uptake via Mas receptor in adipocytes. Acta Diabetol 2012; 49: 291-299 [PMID: 22042130 DOI: 10.1007/s00592-011-0348-z]

110 Santos SH, Braga JF, Mario EG, Rodrigues-Machado Mda G, Murari A, Botion LM, Alenina N, Bader M, Santos RA. Improved lipid and glucose metabolism in transgenic rats with increased circulating angiostatin-(1-7). Arterioscler Thromb Vasc Biol 2010; 30: 953-961 [PMID: 20293301 DOI: 10.1161/ATVBAHA.109.204993]

111 Santos SH, Fernandes LR, Mario EG, Ferreira AV, Pórtio LC, Alvarez-Leite JI, Botion LM, Bader M, Alenina N, Santos RA. Mas deficiency in FVB/N mice produces marked changes in lipid and glycemic metabolism. Diabetes 2008; 57: 340-347 [PMID: 18025412 DOI: 10.2337/db07-0953]

112 Wei Y, Clark SE, Morris EM, Thylfault JP, Uptergrove GM, Whaley-Connell AT, Ferrario CM, Sowers JR, Ibhad JA. Angiostatin II-induced non-alcoholic fatty liver disease is mediated by oxidative stress in transgenic TG(mRen2)27(Ren2) rats. J Hepatol 2008; 49: 417-428 [PMID: 18486983 DOI: 10.1016/j.jhep.2008.03.018]

113 Wei Y, Sowers JR, Nistala R, Gong H, Uptergrove GM, Clark SE, Morris EM, Szary N, Manrique C, Stump CS. Angiostatin II-induced NADPH oxidase activation impairs insulin signaling in skeletal muscle cells. J Biol Chem 2006; 281: 35137-35146 [PMID: 16982630 DOI: 10.1074/jbc.M601320200]

114 Chou CL, Lin H, Chen JS, Fang TC. Renin inhibition improves metabolic syndrome, and reduces angiostatin II levels and oxidative stress in visceral fat tissues in fructose-fed rats. PLoS One 2017; 12: e0180712 [PMID: 28709686 DOI: 10.1371/journal.pone.0180712]

115 Müller JA, Groß R, Conzelmann C, Krüger J, Merle U, Steinhardt J, Weil T, Koepke L, Bozzo CP, Read C, Fois G, Eischel T, Gehrmann J, van Vuuren J, Wessbecher JM, Fricke M, Costa IG, Breunig M, Grüner B, Peters L, Schuster M, Liebisch S, Seufferlein T, Stenger S, Stenzinger A, MacDonald PE, Kirchhoff F, Sparing KMJ, Walther P, Lieckert H, Barth TFE, Wagner M, Milch J, Heller S, Klegler A. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Nat Metab 2021; 3: 149-165 [PMID: 33536639 DOI: 10.1038/s42255-021-00347-1]

116 Leung PS. The physiology of a local renin-angiotensin system in the pancreas. J Physiol 2007; 580: 301-317 [PMID: 17218353 DOI: 10.1113/jphysiol.2006.126193]

117 Fang HJ, Yang JK. Tissue-specific pattern of angiostatin-converting enzyme 2 expression in rat pancreas. J Int Med Res 2010; 38: 558-569 [PMID: 20515560 DOI: 10.1177/0300060510380002018]

118 Shoemaker R, Yiannikouris F, Thatcher S, Cassis L. ACE2 deficiency reduces β-cell mass and impairs β-cell proliferation in obese C57BL/6 mice. Am J Physiol Endocrinol Metab 2015; 309: E621-E631 [PMID: 26389599 DOI: 10.1152/ajpendo.00054.2015]

119 Ramalingam L, Sopontammarak B, Menikdiwela KR, Moustaiz-Moussa N. Endoplasmic Reticulum (ER) Stress in Part Mediates Effects of Angiostatin II in Pancreatic Beta Cells. Diabetes
Inamdar S, Benias PC, Liu Y, Sejpal DV, Satapathy SK, Trindade AJ; Northwell COVID-19 Research Consortium. Prevalence, Risk Factors, and Outcomes of Hospitalized Patients With Coronavirus Disease 2019 Presenting as Acute Pancreatitis. *Gastroenterology* 2020; **159**: 2226-2228.e2 [PMID: 32860787 DOI: 10.1053/j.gastro.2020.08.044]

Lönnrot M, Lynch KF, Elding Larsson H, Lernmark Å, Rewers MJ, Törn C, Burkhardt BR, Briese T, Hagopian WA, She JX, Simell OG, Toppari J, Ziegler AG, Akolkar B, Krischer JP, Hyöty H; TEDDY Study Group. Respiratory infections are temporally associated with initiation of type 1 diabetes autoimmunity: the TEDDY study. *Diabetologia* 2017; **60**: 1931-1940 [PMID: 28770319 DOI: 10.1007/s00125-017-4365-5]

Benyakhlef S, Abdellaoui W, Tahri A, Rouf S, Latrech H. Diabetic Ketoacidosis at Onset of Pediatric Type-1 Diabetes Triggered by Covid-19: An Original Case Report. *Cureus* 2021; **13**: e13958 [PMID: 33880293 DOI: 10.7759/cureus.13958]

Rabizadaeh S, Hajmiri M, Rajab A, Emadi Kouchak H, Nakhjavani M. Severe diabetic ketoacidosis and coronavirus disease 2019 (COVID-19) infection in a teenage patient with newly diagnosed diabetes. *J Pediatr Endocrinol Metab* 2020; **33**: 1241-1243 [PMID: 32809963 DOI: 10.1515/jpem-2020-0296]

Eskandarani RM, Sawan S. Diabetic Ketoacidosis on Hospitalization with COVID-19 in a Previously Nondiabetic Patient: A Review of Pathophysiology. *Clin Med Insights Endocrinol Diabetes* 2020; **13**: 1179551420984125 [PMID: 33488135 DOI: 10.1177/1179551420984125]

Halpert G, Shoenfeld Y. SARS-CoV-2, the autoimmune virus. *Autoimmun Rev* 2020; **19**: 102695 [PMID: 33130000 DOI: 10.1016/j.autrev.2020.102695]

Unsworth R, Wallace S, Oliver NS, Yeung S, Khiarsiagar A, Naidu H, Kwong RMW, Kumar P, Logan KM. New-Onset Type 1 Diabetes in Children During COVID-19: Multicenter Regional Findings in the U.K. *Diabetes Care* 2020; **43**: e170-e171 [PMID: 32816997 DOI: 10.2337/dc20-1551]

Tittel SR, Rosenbauer J, Kamrath C, Ziegler J, Reschke F, Hammersen J, Mönkemöller K, Pappa A, Kapellern T, Holl RW; DPV Initiative. Did the COVID-19 Lockdown Affect the Incidence of Pediatric Type 1 Diabetes in Germany? *Diabetes Care* 2020; **43**: e172-e173 [PMID: 32826282 DOI: 10.2337/dc20-1633]

Hollstein T, Schulte DM, Schulz J, Glück A, Ziegler AG, Bonifacio E, Wendorff M, Franke A, Schreiber S, Bornstein SR, Laudes M. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. *Nat Metab* 2020; **2**: 1021-1024 [PMID: 32879473 DOI: 10.1038/s42255-020-00281-8]
