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Review \ COVID- 19 Pandemic: The Implications for Diabetes Care and Specifics Management

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Abstract: Background. The coronavirus disease 2019 (COVID- 19) pandemic has emerged as one of the greatest challenges faced by humankind in the recent past. People with diabetes and related comorbidities are at increased risk of its complications and of COVID- 19- related death. Older age, multimorbidity, hyperglycemia, cardiac injury and severe inflammatory response are predictors of poor outcome. Aims. This article summarizes current data on the clinical presentation and risks of COVID- 19 in diabetic patients. We also provide some recommendations for the management of diabetic patients with COVID- 19. Results: According. to current data, diabetic patients do not appear to be at increased risk of contracting SARS- CoV- 2 compared to the general population. On the other hand, diabetes is a risk factor for developing severe and critical forms of COVID- 19, the latter requiring admission to an intensive care unit and/or use of invasive mechanical ventilation, with high mortality rates. The characteristics of diabetic patients at risk for developing severe and critical forms of COVID- 19, as well as the prognostic impact of diabetes on the course of COVID- 19, are under current investigation. Obesity, the main risk factor for incident type 2diabetes, is more common in patients with critical forms of COVID- 19 requiring invasive mechanical ventilation. On the other hand, COVID- 19 is usually associated with poor glycemic control and a higher risk of ketoacidosis in diabetic patients. There are currently no recommendations in favour of discontinuing antihypertensive medications that interact with the renin- angiotensin- aldosterone system. Metformin and Sodium- glucose transport protein- 2(SGLT2) inhibitors should be discontinued in patients with severe forms of COVID- 19 owing to the risks of lactic acidosis and ketoacidosis. Conclusion: There are currently no data showing an increased risk of contracting COVID- 19 in diabetic patients. On the other hand, diabetic patients require special attention, since diabetes is associated with a higher risk of severe, critical, and fatal forms of COVID- 19. Our knowledge about this new Coronavirus progresses day by day. Ongoing studies will make it possible to better define the profile(s) of diabetic patients at increased risk of poor prognosis. In any case, the importance of blood glucose monitoring and control over the course of the infection should be emphasized, as well as that of screening for (pre) diabetes in all patients with confirmed infection by COVID- 19.

Keywords: Diabetes, COVID- 19, specifics of management.

مراجعة/ جائحة كوفيد- 19: الآثار المترتبة على رعاية مرضى السكري والمعالجة الخاصة

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الملخص: خلفية: برزت جائحة كرونا لعام 2019 (كوفيد- 19) كواحد من أكبر التحديات التي واجهتها البشرية في الماضي القريب. الأشخاص المصابون بداء السكري والأمراض المصاحبة ذات الصلة معرضون بشكل متزايد لخطر الإصابة بمضاعفاته والوفيات المرتبطة به. الشيخوخة، والأمراض المتعددة، وفرط سكر الدم، وإصابة القلب والاستجابة الالتهابية الشديدة هي مؤشرات على نتائج سيئة على مرضى السكري أثناء جائحة كوفيد- 19. الأهداف: تلخص هذه المقالة البيانات الحالية عن العرض السريري ومخاطر كوفيد- 19 على مرضى السكري. كما نقدم بعض التوصيات لإدارة مرضى السكري أثناء كوفيد- 19 النتائج: وفقًا للبيانات الحالية، لا يبدو أن مرضى السكري معرضون بشكل متزايد لخطر الإصابة بالسارس مقارنة بعامة السكان. من ناحية أخرى فإن مرض السكري هو عامل خطر لتطور الأشكال الحاسمة والخطيرة من كوفيد- 19، وهذا الأخير يتطلب القبول في وحدة العناية المركزة و/ أو استخدام التهوية الميكانيكية الغازية، مع معدلات وفيات عالية. تخضع خصائص مرضى السكري للكشف عن أشكال حادة وحرجة من كوفيد- 19، بالإضافة إلى التأثير النذري لمرض السكري على مسار كوفيد- 19، قيد التحقيق الحالي. السمنة عامل الخطر الرئيسي لمرض السكري من النوع 2، أكثر شيوعًا في المرضى الذين يعانون من أشكال حرجة من كوفيد- 19 التي تتطلب تمدد الوريد الميكانيكي الغزوي. من ناحية أخرى، عادة ما يرتبط كوفيد- 19 بسوء التحكم في نسبة السكر في الدم وارتفاع خطر الإصابة بالحماض الكيتوني لدى مرضى السكري. لا توجد حاليًا توصيات لصالح التوقف عن تناول الأدوية الخافضة للضغط التي تتفاعل مع نظام الرينين- أنجيوتنسين- الألدوستيرون. يجب التوقف عن مثبطات الميتفورمين والبروتين الناقل للصوديوم- جلوكوز في المرضى الذين يعانون من أشكال حادة من كوفيد- 19 بسبب علاجات الحماض اللبني والحماض الكيتوني. الخلاصة: لا توجد بيانات حاليًا تظهر زيادة خطر الإصابة بـ كوفيد- 19 في مرضى السكري. من ناحية أخرى، يحتاج مرضى السكري إلى عناية خاصة، لأن مرض السكري مرتبط بخطر أعلى من الأشكال الحادة والخطيرة والمميتة لـ كوفيد- 19. تتطور معرفتنا بهذا الفيروس التاجي الجديد يومًا بعد يوم، وستتيح الدراسات المستمرة تحديد أفضل لتعريف مرضى السكري المعرضين لخطر متزايد من سوء التشخيص. على أي حال، يجب التأكيد على أهمية مراقبة جلوكوز الدم والسيطرة على مسار العدوى، بالإضافة إلى فحص مرض السكري (قبل) في جميع المرضى الذين يعانون من الإصابة المؤكدة بـ كوفيد- 19.

الكلمات المفتاحية: داء السكري، كوفيد- 19، المعالجة الخاصة.

Introduction

The pandemic of novel "Coronavirus disease 2019" (COVID- 19) challenges both patients and caregivers to ensure continuity of care and to prevent the risks related to various pre- existing chronic conditions. In Yemen, there is no data available for a number of diabetics who were diagnosed with COVID- 19. (1- 3].

In December 2019, a new beta coronavirus causing acute respiratory syndrome emerged from Wuhan in China. Since then, gene sequencing of samples taken from the lower respiratory tract of infected

patients has made it possible to characterize this new virus, called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV- 2). The disease was given the abridged name COVID- 19 by the World Health Organization (WHO) in February 2020. On March 12, 2020, the WHO declared COVID- 19 as a pandemic. The latter has already caused more than 418, 000 deaths worldwide [5]. Two- thirds of which were reported from USA and Brazil, In Yemen, more than 705 cases detected and 160 deaths until June14, 2020, with the numbers are not correct, injuries and deaths are much more according to the reports of the World Health Organization [4, 5].

Coronaviruses are enveloped positive- sense, single- stranded RNA viruses belonging to the Coronaviridae family (subfamily Coro- navirinae, order Nidovirales) including 4 genera (n, |3, and 6) [7]. Most known coronaviruses originate in bats and rodents, as well as in avian species. Six among them are known to cause infections in humans, including the emerging ones, SARS- CoV and MERS- CoV (Middle East Respiratory Syndrome coronavirus), both at the ori- gin of large outbreaks in 2002—2003 and 2012, respectively [6]. Coronaviruses usually cause mild infections in humans, manifesting as a self- limiting flu-1il‹e syndrome whenever the infection is not asymptomatic [6]. However, three emerging coronaviruses (SARS- CoV, MERS- CoV and SARS- CoV- 2) are responsible for severe pneumonia requiring hospitalization and/or admission to an intensive care unit (ICU) and/or use of invasive mechanical ventilation (IMV), with high mortality rates [7]. The mortality rates of the two SARS (2002—2003) and MERS (2012) epidemics reached 10% and 37%, respectively [7].

COVID- 19 is highly transmissible from person to person through respiratory secretions. The virus enters through mucous membranes of the upper respiratory tract, later affecting lungs. [8]. In the majority of cases, COVID- 19 is a mild illness, while some people develop severe disease characterized by respiratory compromise (dyspnoea; respiratory rate ≥ 30 breaths per minute; blood oxygen saturation ≤ 93%; PaO2: FiO2 < 300; and/or pulmonary infiltrates on >50% of lung fields on radiological imaging) [9]. A minority of patients develop critical disease with septic shock or respiratory and/or multi- organ failure. Fewer than 5% of those affected develop serious or critical illness [10], which is likely to be an over-estimate since sub- clinical infection rates in the community are unknown. Secondary pneumonic bacterial infection can be an additional problem.

Owing to the health emergency, knowledge about COVID- 19 is growing rapidly. Diabetes is among the most frequently reported comorbidities in patients infected with COVID- 19. The characteristics of diabetic patients at risk for developing severe and critical forms of COVID- 19, as well as the prognostic impact of diabetes on the course of COVID- 19, are under investigation. Pending for the results of these dedicated studies, this article summarizes current data on the clinical presentation and risks of COVID- 19 in diabetic patients. We also provide some recommendations for the management of diabetic patients with COVID- 19.

Diabetes and infections

Both type 1 and type 2 diabetes increase the susceptibility to infections and their complications [11]. Neutrophil dysfunction, reduced T cell response and disordered humoral immunity are contributory [12], and bacterial and viral respiratory tract infections are particularly common [13]. Diabetes is associated with increased morbidity and mortality risk from pneumonia [14], and hyperglycemia on admission for pneumonia (>11 mmol/l) predicts poor outcome [14]. During the SARS epidemic in 2002/2003, diabetes was an independent predictor of mortality risk (OR 3. 0; 95% CI 1. 4, 6. 3; p = 0. 005) [15]. The presence of comorbidities, including diabetes, also increased mortality risk (independent of age) during the Middle East respiratory syndrome- coronavirus (MERS- CoV) epidemic in 2012 (adjusted HR 3. 74; 95% CI 2. 57, 5. 67) [16]. In another study, diabetes had the strongest impact on mortality risk among MERS- CoV patients [17]. Similarly, among young patients with novel influenza A (H1N1) in 2009, diabetes increased the risk of intensive care unit (ICU) admissions (adjusted OR 4. 72; 95% CI 1. 81, 12. 3) [18].

Are diabetic patients more at risk of contracting COVID- 19?

Testing conditions for diagnosing COVID- 19 infection depend on national policies and capacities. They have changed over time in various countries, making comparisons between available data difficult. Initially, shortage of test reagents prompted Yemini authorities to limit testing to suspected cases of acute infection requiring hospitalization.

Chinese, Italian and American studies showed that diabetes is among the most frequently reported comorbidities in patients infected with COVID- 19, with a prevalence ranging from 3 to 25% in non- critical forms of the infection [19—24]. In meta- analyses of Chinese studies, the mean prevalence of diabetes among patients with COVID- 19 reached 8 to 10% 4 7, 4 8]. In Europe, an Italian team from Padua reported a prevalence of 8. 9% in hospitalized patients with COVID- 19 [25]. These results are comparable to those use- ally observed in the general population of these regions [2], which would suggest that diabetic patients are not at increased risk of contracting COVID- 19.

According to the available evidence, people with diabetes do not have a higher susceptibility to SARS- CoV- 2 infection [25]. However, observations in the recent COVID- 19 pandemic are comparable to those from other epidemics, with higher rates of complications and mortality among patients with diabetes. Hypertension, diabetes, coronary artery disease and cerebrovascular disease were the main associations with severe disease (present in 23. 7%, 16. 2%, 5. 8% and 2. 3%, respectively, of people severely affected by COVID- 19) [26] and mortality rate (53. 8%, 42. 3%, 19. 2% and 15. 4%, respectively, of people who died with the infection) [27].

Immunocompromised state, obesity and tobacco smoking are other risk factors for severe disease and death [8, 28, 29]. A larger study of 72, 314 patients with COVID- 19 in China indicated that patients

with diabetes had a threefold higher mortality rate compared with the mortality rate in COVID- 19 patients overall (7. 3%vs 2. 3%) [30]. In Italy, where the overall case fatality rate is higher (7. 2%, compared with 2. 3% in China), among a group of 355 COVID- 19 fatalities, 35. 5%

had diabetes and 30% had ischemic heart disease [31]. Older age, the presence of two or more comorbidities and obesity also predict poor prognosis among COVID- 19 patients [28, 32]. These are common associations of diabetes and may contribute, at least in part, to the observed increased risk. Nevertheless, in a Chinese study of 1590 COVID- 19 patients, after adjusting for age, smoking and comorbidities, diabetes was an independent risk factor for the composite outcome of increased ICU admission, need for ventilation and death (HR 1. 59; 95% CI 1. 03, 2. 45; p = 0. 037) [21]. So far, no published data are available on disease severity among younger patients with type 1 diabetes, although experts in the field have observed it to be similar to those without [33].

Is diabetes a risk factor of developing severe forms of respiratory distress in COVID- 19?

Regarding viral infections, a recent study showed that diabetes was a risk factor for developing severe and critical pneumonia due to influenza A [34]. The epidemics of SARS and MERS have also shown that diabetic patients and, more broadly, patients with comorbidities such as hypertension, cardiovascular disease and obesity, are at increased risk for developing severe and fatal forms of coronavirus pneumonia [35]. Regarding COVID- 19, it seems already well established that diabetes represents a risk factor or a risk marker for developing severe and critical forms of the infection [36]. Severity criteria, defined by the Chinese National Health Committee, include tachypnea (respiratory rate ≥ 30/minute), oxygen saturation ≤ 93% at rest, and/or an oxygenation index ≤ 300 mmHg and/or lung infiltrates > 50% developing over 24–48 hours. Severe forms require supportive therapy with oxygen, while critical forms include the onset of ARDS (Acute Respiratory Distress Syndrome), shock, and/or multi- organ failure, all requiring admission to an ICU and invasive procedures. These severe and critical forms of COVID- 19 are more frequent in elderly patients (> 60 years) with one or more underlying chronic conditions [37–44]. Beside diabetes, hypertension and cardiovascular disease are the most frequently reported comorbidities [45]. While the prevalence of diabetes among patients with COVID- 19varies from one study to another, reaching that of the general population in certain studies, there are twice as many diabetic patients among those who progress to a severe form of the infection or die from it [25, 36]. According to Chinese data, the prevalence of diabetes in patients with a critical form of COVID- 19 ranges from15 to 25% [41–43]. A prevalence exceeding 50% was even reported in the United States in patients admitted to ICU for a critical form of COVID- 19 [44]. Such data are not yet available. Whereas diabetic patients seem more at risk of developing severe or critical forms of COVID- 19, the respective roles of diabetes per se, chronic hyperglycemia [with glycated hemoglobin (HbA1c) as proxy], insulin deficiency and/or resistance, obesity, and other comorbidities are not yet understood. Only a single study compared the clinical

presentation of COVID- 19 between diabetic (with or without comorbidities) and non- diabetic patients [46]. This Chinese study provided some noteworthy data. First, the infection appears to present initially with milder symptoms in diabetic patients. Thus, fever was less frequent, which could delay initial diagnosis. Second, analysis of chest CT- scans revealed more severe pneumonia in patients with diabetes. Third, diabetic patients (especially those without comorbidity) had more pronounced biological abnormalities, including elevated inflammatory biomarkers [eg. C- reactive protein (CRP) and interleukin 6 (IL6)], elevated tissue enzymes [eg. lactate dehydrogenase (LDH)], and clotting abnormalities (eg. elevated D- dimer). According to the authors, these abnormalities are related to severe multi- organ damage and to a propensity to thromboembolic events, as well as to the "cytokine storm" described as an aggravating factor of COVID- 19 [47]. Finally, lymphopenia, frequently reported as marker of poor prognosis [7, 21, 23], was more frequent and more severe in diabetic patients. Although interesting, these data require confirmation from other studies, including data in other Caucasian and non- Caucasian populations, due to methodological limitations discussed below.

Is diabetes a risk factor for COVID- 19 related death?

Mortality due to COVID- 19 varies from one study to another, ranging from 2 to 15% in severe forms [19–24], to more than 20% and even 50% in critical forms [40- 44]. The overall mortality ascribed to COVID- 19 has been reported jointly for hospitalized and non- hospitalized patients. At the time of writing this article, the case fatality rate in Belgium reached 15% of diagnosed individuals(representing an incidence rate of 68. 7/100, 000 inhabitants); 45%of deaths occurred in hospitals and 55% in home care facilities [4, 5]. Again, these should be interpreted with caution, according to the known limitations regarding screening and diagnostic testing as well as inclusion of suspected yet unconfirmed death cases ascribed to the virus especially in homes care facilities. By comparison, the case fatality rate reached 19% of diagnosed individuals in France (incidence rate of 37. 2/100, 000 individuals), 63% of deaths occurring in hospitals and 37% in home care facilities [4, 48]. How- ever, overall mortality due to COVID- 19 is lower as all affected patients did not undergo testing. According to published data by the European Centre for Disease Prevention and Control, world- wide case fatality rate is currently 7% [4] and universal screening should likely further decrease these estimates.

What about mortality in diabetics? According to Chinese data on more than 70, 000 cases, the overall mortality linked to COVID- 19 was 2. 3% versus 7. 3% in diabetic patients [49]. In addition, the prevalence of diabetes reached 20 to 30% in non- survivors [25, 50]. Diabetic patients clearly appear at increased risk of dying from COVID- 19 [36]. However, the impact of diabetes per seas a prognostic risk factor or marker should be better under- stood, as the majority of patients with severe and critical forms of COVID- 19 had multiple comorbidities also associated with increased odds for developing severe COVID- 19 infection or death [41, 50- 52]. According to Chinese and Italian studies, most of the severely ill or

deceased patients with COVID- 19 had more than 2 or 3 chronic underlying diseases [51, 52]. Guan et al. reported that the odds of severe outcomes including admission to an ICU and/or use of IMV and/or death in patients with COVID- 19 were 1. 79 (95% CI 1. 16–2. 77) among those with at least one comorbidity, and 2. 59 (95%CI 1. 61–4. 17) among those with ≥ 2comorbidities [52]. In the study of Guo et al. [46], diabetic patients died much more often than non- diabetic patients (10. 8% versus 3. 6%). How- ever, mortality rates were similar among non- diabetic and diabetic patients with comorbidities, despite a higher prevalence of cardiovascular disease in the latter (15% versus 32%). On the other hand, diabetic patients without comorbidities died more often than non- diabetic patients (16% versus 0%), with the caveat that they were much older (median age 61 years versus 32 years). The prognostic impact of diabetes should therefore be clarified in more robust studies taking all confounders into account. Why would diabetes per se negatively influence the prognosis of COVID- 19 infection? Diabetes and hyperglycemia were identified as factors that negatively influence the prognosis of sepsis and pneumococcal pneumonia, as well as that of SARS, MERS andH1N1 influenza [35]. The impact of diabetes and obesity was studied in a transgenic mouse model expressing the human DDP- 4, the entry receptor of MERS- CoV [53]. Transgenic diabetic mice with MERS- CoV infection showed more severe viral pneumonia and lung injury characterized by delayed initiation of inflammation and slower inflammatory resolution. These findings suggest that a dysregulated immune response is the basis of increased coronaviruses infection severity in diabetics. In vitro studies showed indeed that hyperglycemia alters innate immunity, induces endothelial function and promotes a pro- coagulant state [54]. In vivo studies also showed that hyperglycemia prolongs the duration of the cytokine response triggered by infection in mouse models of dia- betes [54]. Finally, in vitro hyperglycemia alters the pulmonary epithelium and promotes infection with the influenza virus [54]. Although the clinical relevance of these preclinical data must be confirmed, especially in the context of SARS- CoV- 2 infection, they could explain the severity of the biological and radiological pictured escribed by Guo et al. in diabetic patients with COVID- 19 [46].

Prognostic markers

Similar to previous studies among patients with influenza and bacterial pneumonia, elevated serum ferritin, lactate dehydrogenase, C- reactive protein (CRP), procalcitonin and erythrocyte sedimentation rate (ESR) predicted severe disease among patients with COVID- 19 [23, 55]. This may indicate secondary bacterial infection exacerbating COVID- 19. Increased serum ferritin, in particular, might suggest a severe secondary bacterial infection among these patients, thereby making it useful as a cost- effective prognostic marker [23, 55]. Lymphopenia was also associated with very severe disease [23, 55]. Raised D- dimer levels were observed in severe illness, suggesting a possible consumptive coagulopathy [32], while anticoagulation was linked to decreased mortality rate in COVID- 19 patients [56].

Among 174 COVID- 19 patients, people with diabetes had a greater inflammatory response (higher CRP, ESR and IL- 6, and relative neutrophilia and lymphopenia), higher incidence of coagulopathy (higher D- dimer levels), metabolic derangements (hyperglycemia, transaminitis), severe pneumonia (higher radiological scores) and higher mortality rate, compared with those without [46]. However, people with diabetes in this study were older and had higher prevalence of cardiovascular disease. It is noteworthy that diabetes itself is a proinflammatory and prothrombotic state [57]. The data indicate that COVID- 19, at least in its severe forms, is a state of severe inflammation and thrombotic tendency, so those with diabetes may be predisposed to such intense immune dysfunction resulting in severe late disease.

This is further supported by the observation that renal and cardiovascular comorbidities, which add to the proinflammatory state, further worsen the outcome [46]. Elevated N- terminal pro- brain- type natriuretic peptide (NT- proBNP) and cardiac troponin I (cTnI), were significantly correlated with severe disease, suggesting that COVID- 19 may lead to myocardial injury and impair cardiac function [26]. In people with diabetes and pre- existing ischemic heart disease, limited cardiac reserve may increase morbidity and mortality risk.

What are the consequences of COVID- 19 on diabetes?

Hyperglycemia may precede the symptoms of COVID- 19 and predispose to acute metabolic complications, such as ketoacidosis and hyperosmolar coma. Moreover, COVID- 19 infection can also present with digestive symptoms such as vomiting and diarrhea leading to dehydration. According to Zhou and Tan they including 29 T2DM patients, hyperglycemia was frequent over the course of COVID-19 infection [58]. Another Chinese study showed that COVID- 19 infection was associated with ketoacidosis in 12% of diabetic patients [59]. Hyperglycemia is frequent in critically ill patients resulting from the release of counter- regulatory hormones such as glucagon, cortisol and epinephrine as well as increased circulating levels of proinflammatory cytokines such as interleukin- 6 and tumor necrotic factor-α, which contribute to the cytokine storm and increase insulin resistance [47]. Their action on insulin-sensitive tissues results in decreased muscle glucose uptake, enhanced lipolysis, and increased hepatic glucose output [60].

Given the harmful effects of hyperglycemia (even transient) on innate immunity [54], strict monitoring and control of blood glucose must be part of the management of diabetic patients with COVID- 19. A recently published Chinese study showed that a well- controlled blood glucose, maintaining glycemic variability between0. 70 g/L and 1. 8 g/L, in type 2 diabetic patients with COVID- 19 was associated with a reduction of the 28- day all- cause mortality as well as the a reduction of development of ARDS, acute kidney injury and acute cardiac injury [61]. Although intensive insulin therapy was previously shown to improve both mortality and morbidity of diabetic and non- diabetic patients admitted in the ICU [62], hypoglycemia induced by intensive insulin therapy was identified as an independent risk

factor of death in patients with critical medical conditions including sepsis and bacteremia [63]. The potentially deleterious effects of too tight a glycemic control, predisposing to hypoglycemia in both diabetic and non- diabetic patients admitted to ICU, was further confirmed in multicenter studies [64]. Metformin and SGLT2 inhibitors should be discontinued in severe forms of COVID- 19, given their intrinsic risk of lactic acidosis and ketoacidosis, respectively. Practical recommendations for the management of diabetes in patients with COVID- 19 were recently published [65]. Concerns are also rising regarding the risk of incident diabetes after recovery from mild, asymptomatic or severe COVID- 19 infection. Indeed, it is commonly admitted that certain viral diseases can trigger autoimmune type 1 diabetes in genetically susceptible patients, or even produce fulminant diabetes from mass collapse of cells. COVID- 19 makes use of the Angiotensin Converting Enzyme type 2 (ACE2) receptor as "gateway" to invade target cells in humans [66]. This enzyme is expressed by different tissues and cell types, including the lungs as well as the endocrine pancreas [66]. A study by Yang et al they suggested that infection with SARS- CoV, uses ACE2 as entry receptor, could damage the islets of Langerhans, causing hyperglycemia over the course of infection [67]. Moreover, this study did not demonstrate an increased risk of diabetes in the long term. Another study reported pancreatic injury in COVID- 19 patients were assessed by elevations of plasma amylase and lipase levels in17%, among whom 67% had moderately elevated plasma glucose [68]. The question remains therefore open regarding COVID- 19 and risk of new- onset diabetes. Finally, the hyper- or hypoglycemic impact of treatments administered for the management of COVID- 19 infection must be taken into account, beside the well- known hyperglycemic effect of glucocorticoids. While the benefits and indications of hydroxychloroquine in the treatment of COVID- 19 are still under investigation, it is worth keeping in mind that this molecule as hypoglycemic effects and is used in India as alternative glucose- lowering agent [69]. The mechanisms of hypoglycemia induced by hydroxychloroquine are poorly understood.

Should inhibitors of the renin- angiotensin- aldosterone system (RAAS) be discontinued in diabetic patient with COVID- 19?

While the well- known angiotensin- converting enzyme 1 (ACE1)promotes the conversion of angiotensin I (AT- I) to angiotensin II(AT- II), its homologous counterpart ACE2 is a membrane- bound carboxypeptidase which normally contributes to AT- II inactivation, and therefore physiologically counters RAAS activation [56, 58, 60]. ACE2 also acts as the receptor that allows entry of coronaviruses (SARS- CoV- 2 and SARS- CoV) into human cells [66].

The SARS- CoV- 2 spike- protein, once bound to ACE2, is activated by the type II transmembrane serine protease (TMPRSS2) to pro- mote invasion and viral replication within targets human cells, including type II pneumocytes [66]. ACE inhibitors (ACEI) typically inhibit ACE1 but not ACE2 [70]. On the other hand, ACE2 plays a critical role in maintaining glucose homeostasis and cell function [68, 71].

Preclinical studies have shown that diabetes alters the activity and/or expression of ACE2 in the serum and tissues of different murine models [68, 71, 72]. As an example, a study on rats with streptozotocin-induced diabetes have a reduced pulmonary expression of ACE2 mRNA while NOD mice, developing spontaneously auto- immune diabetes mimicking type 1 diabetes, have increased expression of ACE2 in both the lungs and the heart [68, 72]. Yet, the relevance of such findings in the context of SARS- CoV- 2 infection needs clarification. RAAS inhibitors are widely used in patients with diabetes. RAAS inhibitors might increase the tissue expression of ACE2, thus raising theoretical concerns about increase disinfectivity of SARS- CoV- 2 and poorer prognosis of infected patients on RAAS blockers [73, 74]. Yet, currently published studies did not find increased infectivity of COVID- 19 in patients with previous treatment with RAAS inhibitors. Indeed, a study performed in Italy (Lombardy) including more than 6000 patients, did not find any evidence that RAAS inhibitors affected the risk of COVID- 19 [74]. An observational study, including more than 12, 500 patients tested for COVID- 19 in New York, also did not find an association between previous treatment with RAAS inhibitors and higher risk of testing positive for COVID- 19[75]. Moreover, these molecules could also have beneficial effects in patients with lung injury caused by COVID- 19. Preclinical data showed that mice infected with SARS- CoV and receiving losartan had reduced lung injury compared to untreated mice [35, 73]. This protective effect was associated with an increased expression ofACE2 in response to losartan [35, 73]. In humans, studies reported decreased mortality and lesser requirement of IMV in patients with viral pneumonia receiving RAAS blockers [35]. RAAS blockers could have beneficial immunomodulatory effects at systemic and pulmonary levels by decreasing cytokines [35]. A retrospective Chinese study of 112 patients with prior cardiovascular disease and SARS- CoV- 2 infection showed the same proportion of patients taking RAAS blockers among survivors and non- survivors [76]. The benefit of maintaining RAAS blockers prescribed for chronic cardiovascular and/or chronic renal diseases might exceed their potential harm in patients with COVID-19 as RAAS inhibitors might protect against myocardial injury caused by SARS- CoV- 2 [73]. A recent Chinese study showed a lower risk of all- cause mortality in hospitalized patients with both COVID- 19 and hyper- tension receiving RAAS blockers compared to non- treated patients[66]. Moreover, RAAS inhibitors were not associated with higher risk of severe COVID- 19 neither in Lombardy nor in New- York [75, 77]. Thus, overall, the current recommendation is to continue RAAS inhibitors in both diabetic and non- diabetic patients during acute COVID- 19 infection [73- 75, 77].

Do glucose- lowering drugs impact the pathophysiology of COVID- 19?

Several experimental data suggest that glucose- lowering drugs used in diabetic patients may impact the pathophysiology of SARS- CoV- 2. The glucagon- like peptide- 1 receptor agonist (GLP- 1 RA) liraglutide was shown to counteract the down- regulating effect of diabetes on the pulmonary expression of ACE2 in rats without influencing glucose and insulin levels [68]. GLP- 1- RAs were also shown to have

anti- inflammatory effects and to reduce lung inflammation in murine models of experimental lung injury [68]. In humans, GLP- 1 RAs reduce circulating inflammatory biomarkers in diabetic and/or obese patients while insulin reduces these biomarkers in critically ill patients [68]. Pioglitazone was also shown to upregulate ACE2 in hepatocytes of rats fed a high fat diet [35]. Finally, the dipeptidyl peptidase- 4 (DPP- 4) is the entry receptor of MERS- CoV, raising concerns about the impact of DPP- 4 inhibitors during the course of coronavirus infection [35]. Yet, the clinical relevance of these preclinical and human data in the context of SARS- CoV- 2infection needs clarification [78]. As for the GLP- 1 RA, they have been safely used for blood glucose control in critically ill and ventilated patients in short term studies [58]; but there is insufficient hindsight to recommend their use in diabetic patients with COVID- 19 [78].

Should diabetes be screened in patients with COVID- 19?

T2DM can remain asymptomatic for many years before diagnosis. It is often diagnosed incidentally or at the time of occurrence of chronic complications. Despite the limitations of currently avail- able data regarding the impact of diabetes on the prognosis of COVID- 19, it is plausible that a hither to undiagnosed T2DM, in addition to age and other comorbidities, is a risk factor of poor prognosis. We advise therefore for systematic screening of unrecognized (pre)diabetes, using HbA1c on admission, in all patients hospitalized for COVID- 19, and more broadly, in any patient with proven COVID- 19 infection [79].

Unproven therapies and future directions

In the absence of a specific antiviral drug, anecdotal use of drugs like lopinavir, ritonavir, interferon- 1b, RNA polymerase inhibitor remdesivir, and chloroquine has been reported. 2019- nCoV receptor binding site has a strong affinity with angiotensin converting enzyme 2 (ACE2) and inhibitors of the rennin angiotensin system may have a role in treating severe respiratory disease [80, 81]. Zinc nanoparticles were shown to have inhibitory effects on H1N1 viral load, though their effect in COVID- 19 is unknown and untested [82]. Vitamin C supplementation has some role in prevention of pneumonia and its effect on COVID- 19 needs evaluation [83]. Efforts to develop a vaccine are underway, which will be a major tool to contain this epidemic [84].

Table (1) The use of pharmacotherapies for diabetes and related comorbidities during COVID- 19 [85- 98].

Therapy	Considerations for use during COVID- 19	Suggestions for practice
Metformin	Risk of lactic acidosis in hypoxia and acute illness	Stop if severely ill with haemodynamicinstability or hypoxia
SGLT2inhibitors	Increased risk of dehydration and euglycemicketoacidosis	Stop if oral intake is not tolerated or severely ill
GLP- 1RAs	Gastrointestinal side effects and risk of	Stop in severely ill patients

Therapy	Considerations for use during COVID- 19	Suggestions for practice
	aspiration	
DPP4inhibitors	Low risk of hypoglycemia; possible to use for a wide range of renal function	May be continued in non- critically ill patients
Sulfonylureas	Risk of hypoglycemia if oral intake is poor or with concomitant use of hydroxychloroquine or chloroquine	Stop if unable to maintain regular oral food intake or at risk of hypoglycemia
Pioglitazone	Risk of fluid retention and edema; contraindicated in hemodynamic instability	Stop if severely ill with hemodynamic instability, or hepatic or cardiac dysfunction
Insulin	Requires frequent monitoring due to risk of hypoglycemia	Drug of choice in critically ill patients (see text)
ACEI/ARBs	Uncertain risk of increased susceptibility for infection and uncertain benefit in mitigating inflammatory injury	Continue use unless a specific contraindication arises (hypotension, hyperkaliemia, acute kidney injury)
Aspirin	Risk of cardiovascular disease higher during COVID infection	Continue for patients on aspirin for secondary prevention unless contraindications arise
Statins	Possibility of increased risk of transaminases and myositis	Individualized decision on risk and benefit

Prevention of COVID- 19 in people with diabetes

General precautions are mandatory for patients and caregivers, to prevent contracting COVID- 19 (Text box: General precautions to prevent COVID- 19 in people with diabetes). Chemoprophylaxis (pre- and post- exposure) and vaccines are other strategies under evaluation.

Chemoprophylaxis

No agent had been approved so far for pre- or post- exposure chemoprophylaxis. Evidence from randomized clinical trials are needed. Chloroquine has demonstrated antiviral activity against five out of seven known human coronaviruses, including SARS- CoV- 2 [80] and is a leading candidate for prophylactic used [81]. Ongoing trials in China have yielded encouraging preliminary findings [70], but the data are generally contentious. Other trials are in still in progress: the PHYDRA Trial (NCT04318015) and COPCOV study (NCT04303507). Patients with diabetes included in these studies. A cluster-randomized controlled trial is planned to evaluate the use of lopinavir/ritonavir in post exposure prophylaxis (NCT04321174).

Vaccines

A safe and potent vaccine would obviously be very useful for high risk individuals for develop sever form of SARS- CoV- 2, such as those with diabetes or cardiovascular disease and the elderly. Several vaccines are being investigated: the APICTH trial: recombinant novel coronavirus vaccine (adenovirus type 5 vector) (NCT04313127); mRNA- 1273 vaccine (NCT04283461) and artificial antigen presenting cells (aAPCs) as a vaccine (NCT04299724).

Future directions

COVID- 19 has emerged as one of the greatest challengesfor humankind after the Second World War. For identification of effective preventive and treatment strategies are needed. People with diabetes and related comorbidities have been shown to fare worse, although the pathophysiological and molecular mechanisms behind this link are not yet fully understood. Researchers and authorities worldwide should take urgent steps to answer critical questions in the prevention and management of COVID- 19 and the protection of people with diabetes.

It is imperative to establish standard case definitions, recording and sharing strategies and management guidelines to allow comparison and analysis of data. Standardization of research protocols is essential to utilize time and resources productively. The role of pharmaceutical agents in the prevention and treatment of COVID- 19, in terms of their efficacy, safety and cost effectiveness, should be evaluated as a priority.

Further data are needed, especially looking at the effects of ACEI/ARBs and SGLT2 inhibitors in those infected, also in the severely ill patients. Healthcare systems should adopt strategies for case detection and treatment while maintaining care and supply of essential medicines for people with chronic diseases such as diabetes, to reduce morbidity and mortality risk due to such diseases during this period. The strategic utilization of human resources in healthcare services and safeguarding their health is a timely need. The current challenge for healthcare systems should been opportunity to improve service provision, learn from successful regional and global strategies and prepare for future challenges of greater magnitude. The pandemic also highlights the need for joined- up public health measures and care- for- all policies.

Table (2) General precautions to prevent COVID- 19 in people with diabetes
Hygiene and social distancing: as widely recommended
Glycemic control
Continue regular medication Regular glucose monitoring: consider dose adjustments to match diet and physical activity Ketone level monitoring: in patients with type 1 diabetes or insulin- treated type 2 diabetes, especially if persistently hyperglycemic
Healthy lifestyle

Table (2) General precautions to prevent COVID- 19 in people with diabetes
Healthy diet: ensure regular meals; follow advice for healthy eating in diabetes; limit refined sugars and carbohydrates; consume adequate vegetables, fruit, green leaves and nuts Physical activity: indoor exercise and walking; minimize sedentary/sitting time; online exercise programmers; regular active breaks Avoid smoking; minimize or avoid alcohol Stress management
Comorbidity control and routine vaccinations (pneumococcal and seasonal influenza)

Conclusions.

There are currently no data showing an increased risk of contracting COVID- 19 in diabetic patients. On the other hand, diabetic patients require special attention, since diabetes is associated with a higher risk of severe, critical, and fatal forms of COVID- 19. Knowledge about this new Coronavirus progresses day by day. Ongoing studies will make it possible to better define the profile(s) of diabetic patients at increased risk of poor prognosis. In any case, the importance of blood glucose monitoring and control over the course of the infection should be emphasized, as well as that screening for (pre) diabetes in all patients with confirmed infection by COVID- 19.

Reference

[1]. Sciensano. 2018 Health Interview Survey; 2020 [accessed 14 April2020]https: //his. wiv- isp. be.

[2]. World Health Organization, https: //www. who. int/diabetes/country- profiles, [accessed 14 June 2020].

[3]. International Diabetes Federation, https: //www. diabetesatlas. org, [accessed14 June 2020].

[4]. European Centre For Disease Prevention and Control. https: //www. ecdc. europa. eu, [accessed 14 June 2020].

[5]. Sciensano. Coronavirus COVID- 19; 2020 [accessed 14June 2020]https: //covid19. sciensano. be/fr.

[6]. Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, et al. From SARS to MERS, thrusting Coronaviruses into the spotlight. Viruses 2019;11.

[7]. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel Coronavirus in Wuhan, China. Lancet2020;395: 497–506.

[8]. Lin L, Lu L, Cao W, Li T (2020) Hypothesis for potential pathogenesis of SARS- CoV- 2 infection—a review of immune changes inpatients with viral pneumonia. Emerge Microbes Infect 9(1): 727–732.

[9]. World Health Organization (2020) Report of the WHO–China Joint Mission on coronavirus disease 2019 (COVID- 19). Available fromhttps: //www. who. int/publications- detail/report- of- the- who-chinajoint- mission- on- coronavirus- disease- 2019- (covid- 19). Accessed 14June 2020

[10]. Whitworth J (2020) COVID- 19: a fast evolving pandemic. Trans RSoc Trop Med Hyg 114(4): 241–248.

[11]. Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, CookDG (2018) Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. Diabetes Care41(3): 513–521.

[12]. Geerlings SE, Hoepelman AI (1999) Immune dysfunction inpatients with diabetes mellitus (DM). FEMS Immunol MedMicrobiol 26(3–4): 259–265.

[13]. Peleg AY, Weerarathna T, McCarthy JS, Davis TM (2007) Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. Diabetes Metab Res Rev 23(1): 3–13.

[14]. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schonheyder HC, Sorensen HT (2007) Type 2 diabetes and pneumonia outcomes: apopulation- based cohort study. Diabetes Care 30(9): 2251–2257.

[15]. Yang JK, Feng Y, Yuan MYet al (2006) Plasma glucose levels and diabetes are independent predictors for mortality and morbidity inpatients with SARS. DiabetMed 23(6): 623–628.

[16]. Yang YM, Hsu CY, Lai CC et al (2017) Impact of comorbidity on fatality rate of patients with Middle East respiratory syndrome. SciRep 7(1): 11307.

[17]. Garbati MA, Fagbo SF, Fang VJ et al (2016) A comparative study of clinical presentation and risk factors for adverse outcome inpatients hospitalized with acute respiratory disease due to MERS coronavirus or other causes. PLoS One 11(11): e0165978.

[18]. Allard R, Leclerc P, Tremblay C, Tannenbaum TN (2010) Diabetes and the severity of pandemic influenza A (H1N1) infection. Diabetes Care 33(7): 1491–1493.

[19]. Wang D, Hu B, Zhu F, Liu X, Zhang J, Wang B, et al. Clinical characteristics of138 hospitalized patients with 2019 novel Coronavirus- infected pneumonia in Wuhan, China. JAMA 2020,

[20]. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with Coronavirus disease 2019: retrospective study. BMJ 2020;368.

[21]. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteris- tics of 140 patients infected with SARS- CoV- 2 in Wuhan, China. Allergy 2020.

[22]. Wang X, Fang J, Zhu Y, Chen L, Ding F, Zhou R, et al. Clinical characteristics of non- critically ill patients with novel Coronavirus infec- tion (COVID- 19) in a Fangcang Hospital. Clin Microbiol Infect 2020.

[23]. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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.

[24]. Goyal P, Choi J, Pinheiro L, Schenck E, Chen R, Jabri A, et al. Clini- cal characteristics of COVID- 19 in New York City. N Engl J Med 2020.

[25]. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of dia- betes among people infected with SARS- CoV- 2. J Endocrinal Invest 2020.

[26]. Chen C, Yan JT, Zhou N, Zhao JP, Wang DW (2020) Analysis of myocardial injury in patients with COVID- 19 and associationbetween concomitant cardiovascular diseases and severity ofCOVID- 19. Zhonghua Xin Xue Guan Bing Za Zhi 48(0): E008.

[27]. Guan WJ, Ni ZY, Hu Y et al (2020) Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med.

[28]. Dietz W, Santos- Burgoa C (2020) Obesity and its implications for COVID- 19 mortality. Obesity (Silver Spring).

[29]. Vardavas CI, Nikitara K (2020) COVID- 19 and smoking: a systematic review of the evidence. TobInduc Dis 18: 20

[30]. Wu Z, McGoogan JM (2020) 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. 323(13): 1239.

[31]. Onder G, Rezza G, Brusaferro S (2020) Case- fatality rate and characteristics of patients dying in relation to COVID- 19 in Italy. JAMA.

[32]. Guan WJ, Liang WH, Zhao Y et al (2020) Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. Eur Respir J: 2000547.

[33]. International Society for Paediatric and Adolescent Diabetes (2020)Summary of recommendations regarding COVID- 19 in children with diabetes: keep calm and mind your diabetes care and public health advice. Available from: https: //www. is pad. org/page/Corona virus infection COVID- 19- IIISPAD Summary. Updated 1 June 2020; accessed 14June 2020.

[34]. Zou Q, Zheng S, Wang X, Liu S, Bao J, Yu F, et al. Influenza A- associated severe pneumonia in hospitalised patients: risk factors and NAI treatments. Int J InfectDis2020;92: 208–13.

[35]. Hussain A, Bhowmik B, do Vale Moreira NC. COVID- 19 and diabetes: knowledge in progress. Diabetes Res Clin Pract2020;162: 108142.

[36]. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mor- tality and severity of disease in COVID- 19 pneumonia – a systematic review, meta- analysis, and meta-regression. Diabetes MetabSyndr2020;14: 395–403.

[37]. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel Coronavirus in Wuhan, China. Lancet2020;395: 497–506.

[38]. Wang D, Hu B, Zhu F, Liu X, Zhang J, Wang B, et al. Clinical characteristics of138 hospitalised patients with 2019 novel Coronavirus- infected pneumonia in Wuhan, China. JAMA 2020.

[39]. Goyal P, Choi J, Pinheiro L, Schenck E, Chen R, Jabri A, et al. Clini- cal characteristics of COVID- 19 in New York City. N Engl J Med 2020.

[40]. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical character is- tics of Coronavirus disease 2019 in China. N Engl J Med 2020;382: 1708–20.

[41]. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Corona virus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020.

[42]. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and out comes of critically ill patients with SARS- CoV- 2 pneumonia in Wuhan, China: a single- centered, retrospective, observational study. Lancet Respir Med 2020. ttp: //dx. doi. org/10. 1016/S2213- 2600(20)30079- 5.

[43]. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS- CoV- 2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020.

[44]. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. COVID- 19 in critically ill patients in the Seattle region – Case Series. N Engl J Med 2020.

[45]. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID- 19: prevalence, patho- physiology, prognosis and practical considerations. Diabetes Metab Syndr2020;14: 303–10.

[46]. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID- 19. Diabetes Metab Res Rev 2020: e3319.

[47]. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the "Cytokine Storm" in COVID- 19. J Infect 2020.

[48]. Site du gouvernement franc¸ais, https: //www. gouvernement. fr/info- coronavirus, [accessed 14 June 2020].

[49]. Epidemiology Working Group for NCIP Epidemic Response. The epidemio- logical characteristics of an outbreak of 2019 novel Coronavirus diseases(COVID- 19) in China. Chin J Epidemiol 2020;41: 145–51.

[50]. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID- 19: prevalence, patho- physiology, prognosis and practical considerations. Diabetes Metab Syndr2020;14: 303–10.

[51]. Covid- 19 surveillance group, Italy. https: //www. epicentro. iss. it/en/coronavirus/ bollettino/Report- COVID- 2019 29 april 2020. pdf, [accessed 14June 2020].

[52]. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID- 19 in China: a nationwide analysis. EurRespir J 2020,

[53]. Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity followingMERS- CoV infection. JCI Insight 2019;4.

[54]. Schuetz P, Castro P, Shapiro NI. Diabetes and sepsis: preclinical findings and clinical relevance. Diabetes Care 2011;34: 771–8.

[55]. Chen G, Wu, D, Guo, Wet al (2020) Clinical and immunological features in severe and moderate forms of Coronavirus disease 2019. J Clin Invest 137244. doi: https: //doi. org/10. 1172/JCI137244

[56]. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J ThrombHaemost.

[57]. Tsalamandris S, Antonopoulos AS, Oikonomou E et al (2019) The role of inflammation in diabetes: current concepts and futureperspectives. Eur Cardiol 14(1): 50–59.

[58]. Zhou J, Tan J. Diabetes patients with COVID- 19 need better blood glucose management in Wuhan, China. Metabolism 2020;107: 154216.

[59]. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID- 19 infection may cause ketosis and ketoacidosis. Diabetes ObesMetab 2020.

[60]. Robinson LE, van Soeren MH. Insulin resistance and hyperglycemia in critical ill- ness: role of insulin in glycemic control. AACN Clin Issues 2004;15: 45–62.

[61]. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glu- cose control and outcomes in patients with COVID- 19 and pre- existing type 2diabetes. Cell Metab 2020,

[62]. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, SchetzM, et al. Intensive insulin therapy in critically ill patients. N Engl J Med2001;345: 1359–67.

[63]. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, WoutersPJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med2006;354: 449–61.

[64]. NICE- SUGAR Study Investigators. , Finfer S, Chittock DR, Su SY, Blair D, FosterD, et al. Intensive versus conventional glucose control in critically ill patients. NEngl J Med 2009;360: 1283–97.

[65]. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients withCOVID- 19; 2020,

[66]. Ziegler CGK, Allon S, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, et al. SARS- CoV- 2 receptor ACE2 is an interferon- stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell 2020.

[67]. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol2010;47: 193–9.

[68]. Drucker DJ. Coronavirus infections and type 2 diabetes- shared path- ways with therapeutic implications. Endocr Rev 2020.

[69]. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloro- quine in the treatment of COVID- 19 with or without diabetes: a systematic search and a narrative review with a special reference to India and other developing countries. Diabetes MetabSyndr2020;14: 241–6.

[70]. Alexandre J, Cracowski JL, Richard V, Bouhanick B, Drugs, COVID- 19' working group of the French Society of Pharmacology Therapeutics. Renin- angiotensin- aldosterone system and COVID-19 infection. Ann Endocrinol (Paris) 2020.

[71]. Shoemaker R, Yiannikouris F, Thatcher S, Cassis L. ACE2 deficiency reduces- cell mass and impairs- cell proliferation in obese C57BL/6 mice. Am J Physiol Endocrinol. Metab 2015;309: E621–31.

[72]. Roca- Ho H, Riera M, Palau V, Pascual J, Soler MJ. Characterization of ACE andACE2 expression within different organs of the NOD mouse. Int J Mol Sci2017;18.

[73]. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin- Aldosterone system inhibitors in patients with COVID- 19. N Engl J Med 2020;382: 1653–9.

[74]. 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.

[75]. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, et al. Renin- Angiotensin-Aldosterone system inhibitors and risk of COVID- 19. N EnglJ Med 2020.

[76]. Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patientsinfected by 2019- nCoV. Zhonghua Xin Xue Guan Bing Za Zhi 2020;48: E004, http: //dx. doi. org/10. 3760/cma. j. cn112148- 20200220- 00105 [Chinese].

[77]. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalised with COVID- 19. Circ Res 2020.

[78]. Pal R, Bhadada SK. Should anti- diabetic medications be reconsidered amid COVID- 19 pandemic? Diabetes Res Clin Pract2020;163: 108146.

[79]. Laura O, Michel P, Hermansa, J. T, Dominique M, Bernard V, Jean- Cyr Y. COVID- 19 in diabetic patients: Related risks and specifics of management. Annales d'Endocrinologie 81 (2020) 101–109.

[80]. Sun ML, Yang JM, Sun YP, Su GH. Inhibitors of RAS might Be a good choice for the therapy of COVID- 19 pneumonia. ZhonghuaJiehe He HuxiZazhi 2020 Feb 16;43: E014.

[81]. Phadke M, Saunik S. Use of angiotensin receptor blockers such as Telmisartan, Losartsan in nCoV Wuhan Corona Virus infections e novel mode of treatment. BMJ 2020;368. m406.

[82]. Ghaffari H, Tavakoli A, Moradi A, Tabarraei A, Bokharaei- Salim F, Zahmatkeshan M, Farahmand M, Javanmard D, Kiani SJ, Esghaei M, Pirhajati- Mahabadi V, Monavari SH, Ataei- Pirkooh A. Inhibition of H1N1 influenza virus infection by zinc oxide nanoparticles: another emerging application of nanomedicine. J Biomed Sci 2019;26(1): 70.

[83]. Hemil€a H. Vitamin C intake and susceptibility to pneumonia. Pediatr Infect Dis J 1997 Sep;16(9): 836e7.

[84]. DRAFT landscape of COVID- 19 candidate vaccines d 18 February 2020. Geneva: World health organization. https: //www. who. int/blueprint/priority diseases/ key- action/list- of- candidate-vaccines- developed- against- ncov. pdf. opens in new tab.

[85]. Matthews R (2020) Glucose control key with COVID- 19 in diabetes, say experts. Medscape. Available from https: //www. medscape. com/view article/927044. Accessed 14 June 2020

[86]. Day M (2020) Covid- 19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 368: m1086.

[87]. Wang A, Zhao W, Xu Z, Gu J (2020) Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID- 19) is urgently needed. Diabetes Res Clin Pract 162: 108118.

[88]. Diabetes UK (2020) Updates: Coronavirus and diabetes. Available from: https: //www. diabetes. org. uk/about_us/news/coronavirus. Accessed 13 June 2020

[89]. DeFronzo R, Fleming GA, Chen K, Bicsak TA (2016) Metformin associated lactic acidosis: current perspectives on causes and risk. Metabolism 65(2): 20–29.

[90]. Meyer EJ, Gabb G, Jesudason D (2018) SGLT2 inhibitor associated euglycemic diabetic ketoacidosis: a South Australian clinical case series and Australian spontaneous adverse event notifications. Diabetes Care 41(4): e47–e49.

[91]. Wilding J, Fernando K, Milne N et al (2018) SGLT2 inhibitors in type 2 diabetes management: key evidence and implications for clinical practice. Diabetes The 9(5): 1757–1773.

[92]. Deane AM, Horowitz M (2014) Comment. Is incretin- based therapy ready for the care of hospitalized patients with type 2 diabetes? Diabetes Care 37(2): e40–e41.

[93]. Gomez- Peralta F, Abreu C, Gomez- Rodriguez S, Barranco RJ, Umpierrez GE (2018) Safety and efficacy of DPP4 inhibitor and basal insulin in type 2 diabetes: an updated review and challenging clinical scenarios. Diabetes Ther 9(5): 1775–1789.

[94]. Inzucchi SE, Bergenstal RM, Buse JB et al (2012) Management of hyperglycemia in type 2 diabetes: a patient- centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 55(6): 1577–1596.

[95]. Mendez CE, Umpierrez GE (2015) Pharmacotherapy for hyperglycemia in noncritically ill hospitalized patients. Diabetes Spectr 27(3): 180–188

[96]. American Diabetes Association (2019) 15. Diabetes Care in the Hospital: standards of medical care in diabetes–2019. Diabetes Care 42(Suppl 1): S173–S181.

[97]. Finfer S, Chittock DR, SuSYet al (2009) Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360(13): 1283–1297.

[98]. Moghissi ES, KorytkowskiMT, DiNardoM et al (2009) American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. EndocrPract 15(4): 353–369.

[99]. Gao J, Tian Z, Yang X (2020) Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID- 19 associated pneumonia in clinical studies. Biosci Trends 14(1): 72–73.

[100]. Wang M, Cao R, Zhang L et al (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019- nCoV) in vitro. Cell Res 30(3): 269–271.

[101]. Chang R, Zun W (2020) Repositioning chloroquine as an ideal antiviral prophylaxis against COVID- 19 – time is now. Preprints.