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Review

COVID-19 in diabetic patients: Related risks and specifics of management

COVID-19 chez les patients diabétiques : risques associés et spécificités de prise en charge

Laura Orioli[a,c,*], Michel P. Hermans[a], Jean-Paul Thissen[a,c], Dominique Maiter[a], Bernard Vandeleene[a], Jean-Cyr Yombi[b]

[a] *Department of Endocrinology and Nutrition, Cliniques Universitaires Saint-Luc, avenue Hippocrate 10, 1200 Brussels, Belgium*
[b] *Department of internal medicine, Cliniques Universitaires Saint-Luc, avenue Hippocrate 10, 1200 Brussels, Belgium*
[c] *Department of Endocrinology, Diabetology and Nutrition, IREC, UCLouvain, avenue Hippocrate 55, Brussels, Belgium*

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ABSTRACT

Diabetes is among the most frequently reported comorbidities in patients infected with COVID-19. 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 2 diabetes, 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 SGLT2 inhibitors should be discontinued in patients with severe forms of COVID-19 owing to the risks of lactic acidosis and ketoacidosis. Finally, we advise for systematic screening for (pre)diabetes in patients with proven COVID-19 infection.

Mots clés :
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RÉSUMÉ

Le diabète est l'une des comorbidités le plus fréquemment rapportées chez les patients atteints de COVID-19. Selon les données actuelles, les patients diabétiques ne semblent pas davantage exposés à l'infection par le SARS-CoV-2 que la population générale. En revanche, le diabète apparaît comme un facteur de risque d'évolution vers des formes sévères et critiques de COVID-19. Ces dernières nécessitent une admission aux soins intensifs et/ou le recours à la ventilation mécanique invasive, et sont associées à des taux de mortalité élevés. Les caractéristiques des patients diabétiques à risque de développer une forme sévère ou critique de COVID-19, ainsi que l'impact pronostique du diabète sur l'infection par le SARS-CoV-2, sont en cours d'investigation. L'obésité, principal facteur de risque de survenue d'un diabète de type

* Corresponding author at: Department of Endocrinology and Nutrition, Cliniques Universitaires Saint-Luc, avenue Hippocrate 10, 1200 Brussels, Belgium.
E-mail address: laura.orioli@uclouvain.be (L. Orioli).

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2, est plus fréquente chez les patients atteints de formes critiques requérant un support ventilatoire invasif. D'autre part, le COVID-19 péjore l'équilibre glycémique et favorise la survenue de complications métaboliques telles que l'acidocétose. Au moment de la rédaction de cet article, il n'existe pas de recommandations prônant l'interruption des médications anti-hypertensives qui interagissent avec le système rénine-angiotensine-aldostérone. En raison de leurs risques respectifs d'acidose lactique et d'acidocétose, la metformine et les inhibiteurs du SGLT2 seront interrompus dans les formes sévères de COVID-19. Enfin, nous conseillons un dépistage systématique du (pré)diabète chez les patients présentant une infection par le SARS-CoV-2 démontrée.

1. 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 Belgium, more than half a million people are diagnosed with diabetes mellitus, mostly with type 2 diabetes (T2DM), and at least 20% of them are older than 65 years [1–3]. In France, diabetes affects more than 3 million people, mostly as T2DM, 25% of whom are older than 75 years [2,4]. Furthermore, according to the International Diabetes Federation (IDF), half of all people with T2DM worldwide ignore their condition [3].

In December 2019, a new betacoronavirus 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 characterise 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 Organisation (WHO) in February 2020. On March 12, 2020, the WHO declared COVID-19 as a pandemic. The latter has already caused more than 260,000 deaths worldwide [5]. Two-thirds of which were reported from Europe, where France and Belgium are among the most affected countries, with respectively more than 137,000 and 50,000 cases detected and 25,809 and 8339 deaths on May 7, 2020, with total populations reaching 67 and 11.5 million people, respectively [5,6].

Coronaviruses are enveloped positive-sense, single-stranded RNA viruses belonging to the Coronaviridae family (subfamily Coronavirinae, order Nidovirales) including 4 genera (α, β, γ and δ) [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 origin of large outbreaks in 2002–2003 and 2012, respectively [7]. Coronaviruses usually cause mild infections in humans, manifesting as a self-limiting flu-like syndrome whenever the infection is not asymptomatic [7]. However, three emerging coronaviruses (SARS-CoV, MERS-CoV and SARS-CoV-2) are responsible for severe pneumonia requiring hospitalisation and/or admission to an intensive care unit (ICU) and/or use of invasive mechanical ventilation (IMV), with high mortality rates [8]. The mortality rates of the two SARS (2002–2003) and MERS (2012) epidemics reached 10% and 37%, respectively [9].

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 summarises 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.

1.1. 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 including Belgium, making comparisons between available data difficult. Initially, shortage of test reagents prompted Belgian authorities to limit testing to suspected cases of acute infection requiring hospitalisation. RT-qPCR testing has now been extended to symptomatic caregivers and residents of nursing homes since April 10, 2020, and to any possible case defined by compatible symptoms since May 4, 2020 [6]. Moreover, local procedures have recently included a category of "radiologically confirmed" cases based on suggestive CT-scans [6]. Data released by Sciensano, the Belgian Institute for Health, should thus be interpreted cautiously, according to these limitations in screening and diagnostic procedures. In France, diagnostic testing has been more broadly performed in any symptomatic individual among the caregivers, the elderly, patients with comorbidities and/or patients with respiratory difficulties, as well as hospitalised patients since the epidemic was declared [10]. In April 2020, screening campaigns targeting the elderly people with disabilities as well as their caregivers were also performed. Testing should next be extended to any symptomatic person and their close contacts [10].

In Belgium, comorbidities have been reported only from hospitalised patients most of whom had severe or critical forms of COVID-19 [6]. In these patients, the mean prevalence of pre-existing diabetes reached 21.1% on April 30, 2020 (Table 1). This figure is more than 3-fold higher than the 6% prevalence found in the general adult population (aged ≥ 15 years), reported by both the latest national Health Survey carried out in 2018 [1] and the IDF in 2016 [3]. As expected, the prevalence of diabetes in patients with COVID-19 rises with age but remains higher than that of the 2018 Health Survey (Table 1).

Chinese, Italian and American studies also 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 [11–16]. In meta-analyses of Chinese studies, the mean prevalence of diabetes among patients with COVID-19 reached 8 to 10% [17,18]. In Europe, an Italian team from Padua reported a prevalence of 8.9% in hospitalised patients with COVID-19 [17]. These results are comparable to those usually observed in the general population of these regions [2], which would suggest that diabetic patients are not at increased risk of contracting COVID-19.

Although diabetic patients are considered at higher risk of contracting infections, recent studies have shown that these are mainly fungal and bacterial, particularly soft tissue infections, urinary tract infections and community acquired pneumonia (including pneumococcal pneumonia) [19]. Viral infections, such as seasonal flu, are as frequent in diabetics as in the general population, although diabetes is a risk factor for developing severe or critical forms of these infections [20,21].

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Table 1
Preexisting comorbidities in hospitalised patients with COVID-19 according to age, with a given patient liable to have multiple comorbidities. Data source: Weekly report released by Sciensano on April 30, 2020 including 11,018 patients from February 29 to April 26, 2020 [6].

Age	< 15 (n = 160)	16–44 (n = 1029)	45–64 (n = 3207)	65 (n = 6547)	Total (n = 11,018)	2018 Health Survey[a] [1] (n = 10,000)
Comorbidities	(%)	(%)	(%)	(%)	(%)	(%)
Cardiovascular disease	1.3	3.5	15.3	46.7	32.9	8%[b]
Hypertension	0.6	7.4	26.9	49.8	38.5	18%
Diabetes	0.6	7.1	16.2	26.3	21.2	6%
Obesity	3.6	9.8	13.2	9.0	10.1	16%
Chronic pulmonary disease	1.3	6.1	12.2	17.4	14.5	10%[c]
Chronic kidney disease	0.6	2.4	4.8	17.3	12.1	NR
Cognitive impairment	1.3	2.3	3.1	16.1	10.8	NR
Chronic neurological disease	1.3	2.6	5.5	10.6	8.2	1.4%[d]
Immunodepression, including HIV	2.5	3.6	3.6	2.2	2.7	NR
Chronic liver disease	1.3	1.2	2.8	2.3	2.3	NR
Solid cancer	1.3	1.1	5.3	10.6	8.0	2.4%
Malignant hemopathies	1.3	0.5	1.5	2.2	1.8	
None of the above	87.5	72.8	44.0	12.0	28.1	71%

Detailed clinical data were available in these 11,018 patients who represent 75% of all the patients hospitalised with COVID-19 in Belgium. Data on age were missing in 75 patients. NR: non-reported; HIV: human immunodeficiency virus.
[a] Chronic diseases in the last 12 months.
[b] Includes myocardial infarction, coronary heart disease, other serious heart disease, stroke, narrowing of abdominal and lower limbs arteries.
[c] Includes asthma and chronic obstructive pulmonary disease.
[d] Includes Parkinson's disease and epilepsy.

1.2. Is diabetes a risk factor of developing severe forms of 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 [21]. 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 [9].

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 [18]. Severity criteria, defined by the Chinese National Health Committee, include tachypnea (respiratory rate $\geq$ 30/minute), oxygen saturation $\leq$ 93% at rest, and/or an oxygenation index $\leq$ 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 [8,11–16,22–26]. Beside diabetes, hypertension and cardiovascular disease are the most frequently reported comorbidities (Table 2) [27].

While the prevalence of diabetes among patients with COVID-19 varies 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 [17,18]. According to Chinese data, the prevalence of diabetes in patients with a critical form of COVID-19 ranges from 15 to 25%, a figure 2 to 4-fold higher than that in non-critical patients [22–24]. A prevalence exceeding 50% was even reported in the United States in patients admitted to ICU for a critical form of COVID-19 [26]. Such data are not yet available in Belgium and France.

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 [28]. 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 [33]. Finally, lymphopenia, frequently reported as marker of poor prognosis [8,13,15], 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.

1.3. 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 [11–16], to more than 20% and even 50% in critical forms [22–26]. In Belgium, the overall mortality ascribed to COVID-19 has been reported jointly for hospitalised and non-hospitalised 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 [5,6]. Again, these figures 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 [5,10]. However, 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, worldwide case fatality rate is currently 7% [5] and universal screening should likely further decrease these estimates.

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Table 2
Prevalence of diabetes and other comorbidities in patients with COVID-19 (adapted from Singh AK et al. [27]).

Country, first author	*n*	Patients	Prevalence in the whole cohort (%)					
			HT	Diabetes	Obesity	CVD	COPD	CKD
China								
Huang [8]	41	Critical and non-critical	14.6	19.5	NR	15.0	2.4	NR
Wang [11]	138	Critical and non-critical	31.2	10.1	NR	19.6	2.9	2.9
Chen [12]	274	Moderate, severe and critical	34.0	17.0	NR	8.0	7.0	1.0
Zhang [13]	140	Severe and non-severe	30.0	12.1	NR	8.6	1.4	1.4
Wang [14]	1012	Non-severe, severe and critical	4.5	2.7	NR	1.5	NR	NR
Zhou [15]	191	Non-severe, severe and critical	30.0	19.0	NR	8.0	3.0	1.0
Guan [22]	1099	Non-severe, severe and critical*	15.0	7.4	NR	3.8	1.1	0.7
Wu [23]	201	Critical and non-critical	19.4	10.9	NR	4.0	2.5	1.0
Yang [24]	52	Critical	NR	17.0	NR	23.0	8.0	NR
Guo [28]	187	Hospitalised with pneumonia	32.6	15.0	NR	11.2	2.1	3.2
CCDCP [29]	44,672	Non-severe, severe and critical	12.8	5.3	NR	4.2	2.4	NR
Italy								
Fadini [17]	146	Hospitalised	NR	8.9	NR	NR	NR	NR
Onder [30]	355	Deceased	NR	35.5	NR	42.5	NR	NR
Grasseli [25]	1591	Critical	49.0	17.0	NR	21.0	4.0	3.0
COVID-19 Surveillance group [31]	2351	Deceased	69.2	31.8[b]	11.6	28.2[a]	16.9	21.0
United States								
Goyal [16]	393	Critical and non-critical	50.1	25.2	35.8	13.7	5.1	NR
Bhatraju [26]	24	Critical	NR	58.0	NR	NR	4.00	21.0
CDC COVID-19 response team [32]	7162	Non-severe, severe and critical	NR	10.9	NR	9.0	9.2	3.0
Belgium								
Sciensano [6]	11,018	Hospitalised	38.5	21.2	16	32.9	14.5[c]	12.1

HT: hypertension; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; ICU: intensive care unit; IMV: invasive mechanical ventilation; NR: non-reported; CCDCP: Chinese Centre for Disease Control and Prevention; CDC: Centres for Disease Control and Prevention. Criteria for severe infection were based either on the guideline of the Chinese National Health Committee, the WHO interim guidance or the American Thoracic Society* guidelines for community-acquired pneumonia. Criteria of the Chinese National Health Committee include: respiratory rate $\geq$ 30/minute and/or pulse oximetre oxygen saturation $\leq$ 93% at rest and/or oxygenation index $\leq$ 300 mmHg and/or lung infiltrates > 50% developing over 24–48 hours. Criteria of the WHO include: respiratory rate > 30/minute and/or severe respiratory distress and/or pulse oximetre oxygen saturation $\leq$ 93% at rest. Criteria of the American Thoracic Society* guidelines for community-acquired pneumonia include: minor criteria ($\geq$ 3): respiratory rate > 30/minute, oxygenation index $\leq$ 250 mmHg, multilobar infiltrates, confusion/disorientation, uremia (blood urea nitrogen level $\geq$ 20 mg/dl), leukopenia (white blood cell count < 4000 cells/mL), thrombocytopenia (platelet count < 100,000/ml), hypothermia (core temperature < 36 °C), hypotension requiring aggressive fluid resuscitation and major criteria ($\geq$ 1): septic shock with need for vasopressors or respiratory failure requiring mechanical ventilation. Criteria for critical infection included: admission to the ICU with respiratory failure, need for invasive, mechanical ventilation, shock, failure of organs.

[a] Chronic pulmonary diseases.

[b] Type 2 diabetes.

[c] Ischemic heart disease.

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 [29]. In addition, the prevalence of diabetes reached 20 to 30% in non-survivors, a figure up to 3-fold higher than that in surviving patients [17,27]. The prevalence of outcomes in diabetic patients including severe disease, admission to an ICU and death are shown in Fig. 1. Such data are not yet available in France and Belgium.

Diabetic patients clearly appear at increased risk of dying from COVID-19 [18]. However, the impact of diabetes per se as a prognostic risk factor or marker should be better understood, 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 [23,27,31,34]. 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 [31,34]. 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 $\geq$ 2 comorbidities [34].

In the study of Guo et al. [28], diabetic patients died much more often than non-diabetic patients (10.8% versus 3.6%). However, 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 and H1N1 influenza [9]. The impact of diabetes and obesity was studied in a transgenic mouse model expressing the human DDP-4, the entry receptor of MERS-CoV [35]. Transgenic diabetic mice with MERS-CoV infection showed more severe viral pneumonia and lung injury characterised 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 dysfunction and promotes a pro-coagulant state [19]. In vivo studies also showed that hyperglycemia prolongs the duration of the cytokine response triggered by infection in mouse models of diabetes [19]. Finally, in vitro hyperglycemia alters the pulmonary epithelium and promotes infection with the influenza virus [9]. 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 picture described by Guo et al. in diabetic patients with COVID-19 [28].

1.4. Do all diabetic patients with COVID-19 have the same risks?

From a diabetologist's point of view, the studies published to date did not provide data on the type and duration of diabetes,

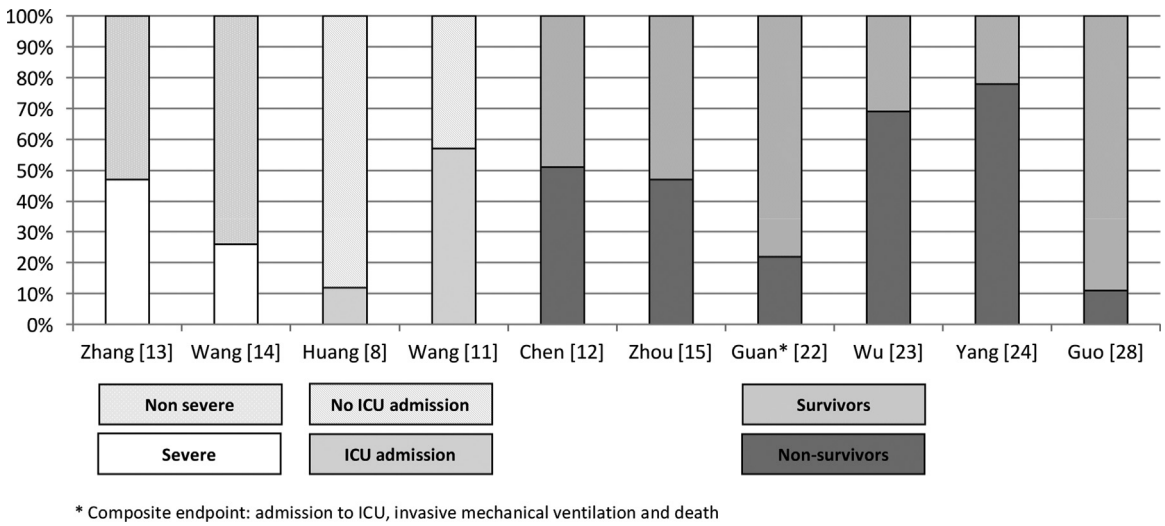

Fig. 1. Prevalence of outcomes in diabetic patients with COVID-19 (Chinese data).

glucose-lowering drugs, and chronic glycemic control (HbA1c) prior to admission. These data would make it possible to identify among diabetic patients those at higher risk of developing severe and critical forms of COVID-19. Of ongoing studies, the CORONADO survey (Coronavirus SARS-CoV2 and Diabetes Outcomes) should provide these much-needed data. This French multi-centre study, supported by the French-speaking Diabetes Society (Société Francophone du Diabète, SFD), was recently launched and will include more than 300 diabetic patients. One may however anticipate that older and/or obese patients with poorly controlled T2DM and/or micro- and macrovascular complications should be more severely affected by COVID-19 than younger patients with uncomplicated diabetes and good glycemic control.

Obesity, a major risk factor for incident T2DM, was already reported to be a risk factor of poor prognosis in patients with COVID-19. The higher mortality rates related to COVID-19 reported in Italy (compared to those in China) could be explained, at least in part, by a higher prevalence of obesity in elderly patients from the peninsula [36]. Indeed, a Chinese study found that the body mass index (BMI) of critically ill patients with COVID-19 was higher than that of non-critical patients (25.5 kg/m^2 versus 22.0 kg/m^2) [37]. Moreover, the prevalence of overweight and obesity in this study was higher in non-survivors compared to survivors (88% versus 19%) [37]. Another Chinese study (not peer-reviewed at the time of writing this report) reported that overweight and obesity might be associated with an increased risk of developing severe pneumonia in patients with COVID-19 [38]. These associations might be more pronounced in men in whom overweight and obesity were respectively associated with a 1.96-fold and 5.7-fold increased risk, compared to a 1.51-fold and a 0.71-fold risk in women [38]. A French study (Lille) showed a high prevalence of obesity (48%) among patients with COVID-19 admitted to the ICU as well as an increasing requirement of IMV according to BMI [39]. In this study, 86% of patients with severe or morbid obesity (BMI $\geq$ 35 kg/m^2) required IMV, against 47% of patients with normal weight (BMI < 25 kg/m^2). In Belgium, the mean prevalence of obesity in hospitalised patients with COVID-19 reached 10.5% (Table 1), a figure surprisingly lower than the 16% prevalence found in the general population, as reported in the 2018 Health Survey [1,6]. In contrast, obesity was reported in 36% to 50% of hospitalised patients with COVID-19 in the United States [16,40,41] whereas the prevalence of obesity reached 35% in the general population in 2016 according to the WHO [2]. In Italy, the prevalence of obesity and T2DM among patients who died from COVID-19 did not differ between women and men, respectively 31.4% versus 31.9% and 12.7% versus 11.0% [31]. The prevalence of body weight excess (BMI $\geq$ 25 kg/m^2 in Caucasians, BMI $\geq$ 24 kg/m^2 in Asian) in COVID-19 patients has been infrequently reported up to now, reaching 42.7% in China [38,not peer-reviewed], 81.4% in the United States [41] and 74.8% in the United Kingdom [42] compared to 35.4%, 69.6% and 66.7%, respectively, in the general population of these countries [2]. A first link between body weight excess and severity of COVID-19 infection is the negative impact of obesity on the pulmonary function, including reduced expiratory reserve, functional capacity, and respiratory system compliance; as well as decreased diaphragmatic movements with abdominal obesity in supine position [36]. Inflammation might be a second link between obesity and severe forms of COVID-19. Indeed, the risk for developing ARDS as well as the outcomes of ARDS have been linked to a series of genes and their variants including those coding for pro-inflammatory cytokines (such as IL-6), chemokines and ACE [45] while obesity is associated with low-grade systemic inflammation and elevated plasma levels of pro-inflammatory cytokines (such as IL-6) and complement overactivation [36]. Moreover, epicardial fat whose volume is increased in obese individuals and lung adipocytes might play a role in cardiac and lung injuries caused by COVID-19 [46,47]. Available data regarding obesity in patients with COVID-19 are summarised in Table 3.

1.5. 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 a Chinese study including 29 T2DM patients, hyperglycemia was frequent over the course of COVID-19 infection [48]. Another Chinese study showed that COVID-19 infection was associated with ketoacidosis in 12% of diabetic patients [49]. Hyperglycemia and insulin resistance are frequent in critically ill patients. They result from the release of counter-regulatory hormones such as glucagon, cortisol and epinephrine as well as increased circulating levels of proinflammatory cytokines such as IL-6 and TNFa, which contribute to the cytokine storm [33]. Their action on insulin-sensitive tissues results in decreased muscle glucose uptake, enhanced lipolysis, and increased hepatic glucose output [50].

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Table 3
Prevalence of obesity in patients with COVID-19 according to outcomes.

Country, first author	*n*	Obesity	Outcomes	No ICU/No IMV/Survivors/Non-severe	ICU/IMV/Non-survivors/severe	*P* value/OR (CI)
France						
Simonnet [39]	124	47.6% BMI ≥ 30 28.2% BMI ≥ 35	IMV	28.2% BMI ≥ 30 12.8% BMI ≥ 35	56.4% BMI ≥ 30 35.3% BMI ≥ 35	< 0.01 < 0.01
Caussy [43]	291	11.3% BMI ≥ 35	IMV	41.9% BMI < 25	81.8% BMI ≥ 35	0.001
Italy						
COVID-19 Surveillance group [31]	2351	11.6%[a]	Death	NR NR	In women 12.7% In men 11.0%	NR NR
United Kingdom						
ICNARC report [42]	7542	38.8% BMI ≥ 30	IMV[b] Death	37.9% BMI ≥ 30 38.9% BMI ≥ 30	39.0% BMI ≥ 30 37.5% BMI ≥ 30	NR NR
United States						
Goyal [16]	380	35.8% BMI ≥ 30	IMV	31.9% BMI ≥ 30	43.4% BMI ≥ 30	NR
Kalligeros [41]	103	21.3% BMI 30–34 26.2% BMI ≥ 35	ICU	18.6% BMI 30–34 22.0% BMI ≥ 35	25.0% BMI 30–34 31.8% BMI ≥ 35	2.56 (0.64–10.1), 0.100 6.16 (1.42–26.66), 0.015
Lighter [44]	3615	21% BMI 30–34 16% BMI ≥ 35	ICU	NR NR NR NR	22% of BMI 30–34 ≥ 60 y 19% of BMI ≥ 35 ≥ 60 y 23% of BMI 30–34 < 60 y 33% of BMI ≥ 35 < 60 y	1.1 (0.8–1.7), 0.57 1.5 (0.9–2.3), 0.10 1.8 (1.2–2.7), 0.006 3.6 (2.5–5.3), < 0001
China						
Peng [37]	112	N/A	Death	19% BMI ≥ 25[c]	88% BMI ≥ 25[c]	0.001

BMI: body mass index; IMV: invasive mechanical ventilation; ICU: intensive care unit; N/A: non-available; NR: non-reported; y: years; OR: Odds Ratio; CI: confidence interval; ICNARC: Intensive Care National Audit and Research Centre.

[a] Obesity not defined.

[b] Advanced respiratory support included: invasive ventilation, BPAP via trans-laryngeal tube or tracheostomy, CPAP via trans-laryngeal tube, extra-corporeal respiratory support.

[c] BMI between 24 and 27 kg/m^2 should be considered as overweight and BMI ≥ 28 as obesity in Asian people according to World Health Organisation cut-offs.

Given the harmful effects of hyperglycemia (even transient) on innate immunity [19], 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 between 0.70 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 [51]. Although intensive insulin therapy was previously shown to improve both mortality and morbidity of diabetic and non-diabetic patients admitted in the ICU [52], 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 [53]. 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 multicentre studies [54]. 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 [55].

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 β cells. COVID-19 makes use of the Angiotensin Converting Enzyme type 2 (ACE2) receptor as "gateway" to invade target cells in humans [56]. This enzyme is expressed by different tissues and cell types, including the lungs as well as the endocrine pancreas [56]. A Chinese study has suggested that infection with SARS-CoV, which also uses ACE2 as entry receptor, could damage the islets of Langerhans, causing hyperglycemia over the course of infection [57]. In contrast, this study did not demonstrate an increased risk of diabetes in the long term. Another Chinese study reported pancreatic injury assessed by elevations of plasma amylase and lipase levels in 17% of patients with COVID-19, among whom 67% had moderately elevated plasma glucose [58]. 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 has hypoglycemic effects and is used in India as alternative glucose-lowering agent [59]. The mechanisms underlying this hypoglycemic effect are poorly understood; a series of complex molecular effects may both improve insulin sensitivity and insulin secretion. The dosages of glucose-lowering drugs, including insulin, should be adjusted accordingly.

1.6. 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 emergent coronaviruses (SARS-CoV-2 and SARS-CoV) into human cells [56].

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The SARS-CoV-2 spike-protein, once bound to ACE2, is activated by the type II transmembrane serine protease (TMPRSS2) to promote invasion and viral replication within targets human cells, including type II pneumocytes [56]. ACE inhibitors (ACEI) typically inhibit ACE1 but not ACE2 [61]. On the other hand, ACE2 exerts a critical role in maintaining glucose homeostasis and β-cell function [58,62]. Preclinical studies have shown that diabetes alters the activity and/or expression of ACE2 in the serum and tissues of different murine models [58,62,63]. As an example, 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 [58,63]. 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 and hypertension. RAAS inhibitors might increase the tissue expression of ACE2, thus raising theoretical concerns about increased infectivity of SARS-CoV-2 and poorer prognosis of infected patients on RAAS blockers [60,64]. Yet, currently published studies did not find increased infectivity of COVID-19 in patients with previous treatment with RAAS inhibitors. Indeed, a population-based case-control study performed in Italy (Lombardy) including more than 6000 patients, did not find any evidence that RAAS inhibitors affected the risk of COVID-19 [64]. 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 [65]. 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 [9,60]. This protective effect was associated with an increased expression of ACE2 in response to losartan [9,60]. In humans, studies reported decreased mortality and lesser requirement of IMV in patients with viral pneumonia receiving RAAS blockers [9]. RAAS blockers could have beneficial immunomodulatory effects at systemic and pulmonary levels by decreasing cytokines [9]. 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 [37]. 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 organ injury including myocardial injury caused by SARS-CoV-2 [60]. A recent Chinese study showed a lower risk of all-cause mortality in hospitalised patients with both COVID-19 and hypertension 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 [64,65]. Thus, overall, the current recommendation is to continue RAAS inhibitors in both diabetic and non-diabetic patients during acute COVID-19 infection [60,64–66].

1.7. 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 COVID-19. The glucagon-like peptide-1 receptor agonist (GLP-1 RA) liraglutide was shown to counteract the downregulating effect of diabetes on the pulmonary expression of ACE2 in rats without influencing glucose and insulin levels [58]. GLP-1-RAs were also shown to have anti-inflammatory effects and to reduce lung inflammation in murine models of experimental lung injury [58]. In humans, GLP-1 RAs reduce circulating inflammatory biomarkers in diabetic and/or obese patients while insulin reduces these biomarkers in critically ill patients [58]. Pioglitazone was also shown to upregulate ACE2 in hepatocytes of rats fed a high fat diet [9]. 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 [9]. Yet, the clinical relevance of these preclinical and human data in the context of SARS-CoV-2 infection needs clarification [67]. 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 [67].

1.8. 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 available data regarding the impact of diabetes on the prognosis of COVID-19, it is plausible that a hitherto undiagnosed T2DM, in addition to age and other comorbidities, is a risk factor of poor prognosis. We advise therefore for systematic screening of unrecognised (pre)diabetes, using HbA1c on admission, in all patients hospitalised for COVID-19, and more broadly, in any patient with proven COVID-19 infection.

2. 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. 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 emphasised, as well as that of screening for (pre)diabetes in all patients with confirmed infection by COVID-19.

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The authors declare that they have no competing interest.

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