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COVID-19 and diabetes mellitus: management of patients during the pandemic

Abstract. *Coronavirus disease 2019 (COVID-19) is a potentially severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). People with diabetes mellitus (DM) are at increased risk of serious illness from COVID-19. DM and uncontrolled glycemia were reported as significant predictors of severity and deaths in patients infected with different viruses, including the 2009 pandemic influenza A (H1N1), SARS-CoV and MERS-CoV. In the current SARS-CoV-2 pandemic, some studies did not find a clear association between DM and disease severity. However, other reports from China and Italy showed that older patients with chronic diseases, including DM, were at higher risk for severe COVID-19 and mortality. Among COVID-19 mortality cases in Wuhan, China, major associated comorbidities include DM (42.3 %), hypertension (53.8 %), previous heart disease (19.2 %) and cerebral infarction (15.4 %). Also, mortality strongly increased with the presence of DM (7.3 %) and other comorbidities like cardiovascular disease (10.5 %), chronic respiratory disease, hypertension and cancer, each at 6 %. According to several studies, the prevalence of DM in people infected with the virus is about the same as in the general population, even slightly lower. A meta-analysis of 12 studies describing data from 2,108 Chinese patients with COVID-19 reported a diabetes prevalence of 10.3 %, which was similar to the national prevalence of 10.9 % reported in 2013. Patients with DM are advised to follow general guidance on risk reduction and also specific to DM. All current recommendations of healthcare organizations and scientific communities emphasise the importance of good glycemic control during the COVID-19 pandemic as it may help in reducing the risk of infection and severity.*
Keywords: *diabetes mellitus; COVID-19*

Background

Coronavirus disease 2019 (COVID-19) is a potentially severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). People with diabetes mellitus (DM) are at increased risk of serious illness from COVID-19. Understanding this risk and the best ways to mitigate it is a key to enabling patients, carers, and healthcare professionals to make informed choices about ways to manage DM during the COVID-19 pandemic [1—4].

Current evidence

DM and uncontrolled glycemia were reported as significant predictors of severity and deaths in patients infected with different viruses, including the 2009 pandemic influenza A (H1N1), SARS-CoV and MERS-CoV. In the current SARS-CoV-2 pandemic, some studies did not find a clear association between DM and disease severity [5]. However, other reports from China [6, 7] and Italy [8] showed that older patients with chronic diseases, including DM, were at higher risk for severe COVID-19 and mortality [4].

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DM is a chronic inflammatory condition characterized by multiple metabolic and vascular abnormalities that can affect the response to pathogens. Hyperglycemia and insulin resistance promote increased synthesis of glycosylation end products and pro-inflammatory cytokines, oxidative stress, in addition to stimulating the production of adhesion molecules that mediate tissue inflammation. This inflammatory process may compose the underlying mechanism that leads to a higher propensity for infections, with worse outcomes thereof in patients with DM [4].

Among COVID-19 mortality cases in Wuhan, China, major associated comorbidities included DM (42.3 %), hypertension (53.8 %), previous heart disease (19.2 %) and cerebral infarction (15.4 %). Also, mortality strongly increased with the presence of DM (7.3 %) and other comorbidities like cardiovascular disease (10.5 %), chronic respiratory disease, hypertension and cancer, each at 6 % (Fig. 1) [2].

Today, suggestions are made on the possible pathological mechanisms of the relationship between DM and COVID-19. However, no definite conclusions can be made based on current limited evidence [4].

Scarce data exist regarding glucose metabolism and the development of acute complications of DM (e.g., ketoacidosis — DKA) in patients with COVID-19. Infection of SARS-CoV-2 in those with DM possibly triggers higher stress conditions, with the greater release of hyperglycemic hormones, e.g., glucocorticoids and catecholamines, leading to increased blood glucose levels and abnormal glucose variability [9].

On the other hand, a retrospective study from Wuhan reported that around 10 % of the patients with type 2 DM and COVID-19 suffered at least one episode of hypoglycemia (< 3.9 mmol/l) [10]. Hypoglycemia has been shown to mobilize pro-inflammatory monocytes and increase platelet reactivity, contributing to higher cardiovascular mortality in patients with diabetes [11].

Yet it remains largely unknown how exactly the inflammatory and immune response occurs in these patients, as well as whether hyper- or hypoglycemia may alter the SARS-CoV-2 virulence, or the virus itself interferes with insulin secretion or glycemic control. Furthermore, the impact of usual diabetes drug treatment on COVID-19 outcomes, as well as therapeutic approaches for COVID-19 on glucose regulation remains unspecified [4].

In addition, COVID-19 with diabetes mellitus has much more potential to progress rapidly with acute respiratory distress syndrome and septic shock, which may be eventually followed by multiple organ failure [5, 9].

According to several studies, the prevalence of DM in people infected with the virus is about the same as in the general population, even slightly lower [12, 13]. A meta-analysis of 12 studies describing data from 2,108 Chinese patients with COVID-19 reported a diabetes prevalence of 10.3 % [13], which was similar to the national prevalence of 10.9 % reported in 2013.

Measures in diabetic patients

Patients with DM are advised to follow general guidance on risk reduction and also specific to DM. All current recommendations of healthcare organizations and scientific communities emphasise the importance of good glycemic control during the COVID-19 pandemic as it may help in reducing the risk of infection and severity [2, 3, 14, 15].

Specific measures in diabetic patients

— More frequent blood glucose monitoring (in people who self-monitor).

— To take influenza and pneumonia vaccinations as offered.

— Patients with DM with coexisting heart or kidney disease require special care to stabilise their cardiac/renal status [3, 15].

General preventive measures

Thorough handwashing with soap and water should be encouraged since it kills the virus. Use of alcohol-based hand rubs is also healthy.

There is a need to practise proper respiratory hygiene with covering of mouth and nose with bent elbow or tissue when coughing or sneezing. Touching of mouth, nose and eyes should be avoided.

Contact with an affected person needs to be minimised. Use of recommended face masks is advised if there is a contact with someone with respiratory symptoms.

Non-essential travel to major affected areas should be avoided in order to restrict the spread of infection [1, 15].

Management of patients with diabetes mellitus and COVID-19
Medication management

Medication management is a key issue for patients with DM when unwell. It is unclear if there are specific considerations related to COVID-19. A narrative review (not systematic) of clinical considerations for DM during COVID-19 [3] suggests that:

— anti-hyperglycemic agents that can cause volume depletion or hypoglycemia should be avoided;
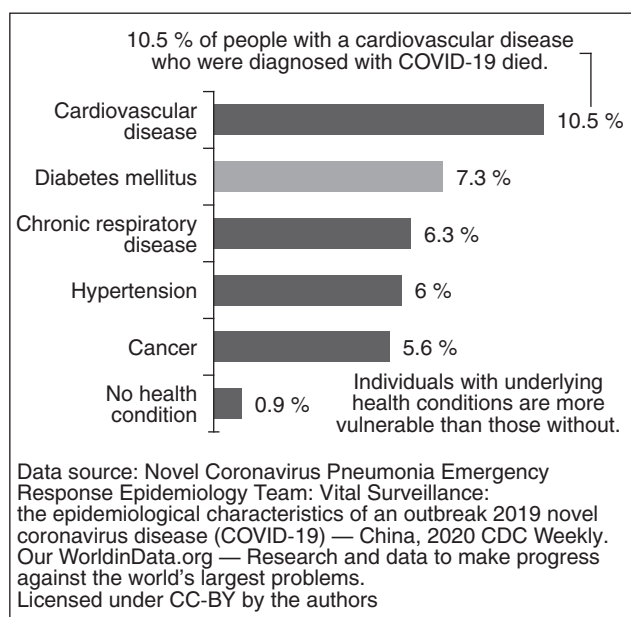

Data source: Novel Coronavirus Pneumonia Emergency Response Epidemiology Team: Vital Surveillance: the epidemiological characteristics of an outbreak 2019 novel coronavirus disease (COVID-19) — China, 2020 CDC Weekly. Our WorldinData.org — Research and data to make progress against the world's largest problems. Licensed under CC-BY by the authors

Figure 1. Coronavirus: early-stage case fatality rates by underlying health condition in China

— dosage of oral anti-diabetic drugs may need to be reduced;

— oral agents especially metformin and sodium-glucose cotransporter-2 inhibitors (SGLT2) need to be stopped;

— insulin is the preferred agent for control of hyperglycemia in hospitalised sick patients.

Diabetes UK also emphasises the need to discontinue *SGLT2 inhibitors* when unwell (dapagliflozin, canagliflozin, empagliflozin) [15]. This may be due to an increased risk of euglycemic DKA and dehydration [16].

However, it should be noted that the question of the use of metformin in patients with DM and COVID-19 is still debatable. Practitioners have often avoided the use of *metformin* in patients at risk of hypoxia due to a potential risk of lactic acidosis even though metformin is rarely associated with lactic acidosis. But, on the other hand, that its risk is minimal and does not exceed the benefits of metabolic effects [17]. Moreover, metformin is included in the list of sixty-nine drugs and experimental compounds, that may be effective in treating COVID-19 based on molecular effects [18].

Noteworthy is the fact that dipeptidyl-peptidase-4 (DPP-4) is the primary receptor of MERS-CoV [19]. Since *DPP-4 inhibitors* are commonly applied in the treatment of diabetes worldwide, future research should explore whether DPP-4 may also act as a receptor for SARS-CoV-2, thus contributing to a potential protective effect of these drugs against COVID-19 [20].

ACE inhibitors are prescribed for many people with DM to prevent or control diabetic complications; it has been suggested that these have the potential to both benefit and cause harm in COVID-19 [3]. Nevertheless, a retrospective analysis performed on 112 patients with COVID-19 and CVD did not show a significant difference in the proportion of ACEI/ARB medication between survivors and non-survivors [21].

It should be noted that today, "there is no specific medicine recommended to prevent or treat the new coronavirus", according to the World Health Organization (WHO). "Some specific treatments are under investigation and will be tested through clinical trials," the WHO said [22].

Management in the community

Management in the community has been covered by recent guidance and generally follows standard sick-day rules for patients with DM.

Advice is also offered for patients with DM experiencing symptoms of COVID-19 [3, 14, 15]. Those specific to patients with DM include:

— following advice of diabetes care provider;

— checking blood sugar more frequently for people who routinely check their blood sugar level at home (every 4 hours including at night at type 1 DM);

— testing for ketones;

— contacting healthcare provider if the blood sugar level is high or if ketones are present;

— being aware of the signs of hyperglycemia for those who don't routinely test at home and contacting a healthcare provider if experiencing symptoms;

— staying hydrated;

— trying to eat or have drinks with carbohydrates for energy;

— getting medical help as soon as possible if vomiting or not able to keep fluids down [3, 14].

It is noticed that atypical ketosis was observed in type 2 DM; fluid replacement may need to be tempered during DKA management due to risk of ARDS; in a subset in a ventilated cohort high doses of insulin were required to manage hyperglycemia; and as patients often need to be nursed prone, which interrupts feeding, there is paradoxically also a risk of hypoglycemia [3, 14, 15].

Post-discharge, they recommend blood glucose homeostasis be maintained continuously for 4 weeks and advise that patients need to avoid infectious diseases due to a lower immune response [3, 14].

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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COVID-19 і цукровий діабет:
менеджмент пацієнтів під час пандемії

Резюме. Коронавірусна хвороба 2019 (COVID-19) — потенційно тяжка гостра респіраторна інфекція, спричинена коронавірусом-2 (SARS-CoV-2), із вираженим гострим респіраторним синдромом. Люди з цукровим діабетом (ЦД) мають підвищений ризик виникнення серйозних розладів на тлі COVID-19. У статті повідомляється, що ЦД і неконтрольована глікемія є важливими предикторами тяжкості перебігу і смерті серед пацієнтів, інфікованих різними вірусами, включаючи пандемічний грип А (H1N1) у 2009 році, SARS-CoV і MERS-CoV. У триваючій пандемії SARS-CoV-2 у деяких дослідженнях не виявлено чіткого зв'язку між ЦД і тяжкістю захворювання. Однак аналіз даних із Китаю та Італії показав, що пацієнти похилого віку із хронічними захворюваннями, включаючи ЦД, зазнають більшого ризику тяжкої COVID-19 та смертності. Серед випадків смертності від COVID-19 в Ухані (Китай) основними супутніми захворюваннями були ЦД (42,3 %), артеріальна гіпертензія (53,8 %), захворювання серця в анамнезі (19,2 %) та церебральні розлади (15,4 %). Також смертність істотно зростає (на 6 %) за наявності ЦД (7,3 %) та інших супутніх захворювань, таких як серцево-судинні (10,5 %), хронічні захворювання органів дихання, артеріальна гіпертензія та рак. За даними досліджень, поширеність ЦД у людей, заражених вірусом, приблизно така ж, як і в загальній популяції, навіть дещо нижча. За результатами метааналізу 12 досліджень, які описують дані 2108 китайських пацієнтів із COVID-19, поширеність ЦД становила 10,3 %, що було аналогічно поширеності 10,9 % в 2013 році. Пацієнтам із ЦД рекомендується дотримуватися загальних порад щодо зменшення ризику зараження, а також специфічних для людей з ЦД. Усі сучасні рекомендації медичних організацій та наукових спільнот підкреслюють важливість належного контролю глікемії під час пандемії COVID-19, оскільки це може допомогти зменшити ризик зараження та тяжкість хвороби.

Ключові слова: цукровий діабет; COVID-19

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COVID-19 и сахарный диабет:
менеджмент пациентов во время пандемии

Резюме. Коронавирусная болезнь 2019 (COVID-19) — потенциально тяжелая острая респираторная инфекция, вызванная коронавирусом-2 (SARS-CoV-2), с выраженным острым респираторным синдромом. Люди с сахарным диабетом (СД) имеют повышенный риск возникновения серьезных расстройств на фоне COVID-19. В статье сообщается, что СД и неконтролируемая гликемия являются важными предикторами тяжести и смерти среди пациентов, инфицированных различными вирусами, включая пандемический грипп А (H1N1) в 2009 году, SARS-CoV и MERS-CoV. В условиях продолжающейся пандемии SARS-CoV-2 в некоторых исследованиях не выявлено четкой связи между СД и тяжестью заболевания. Однако анализ данных из Китая и Италии показал, что пациенты пожилого возраста с хроническими заболеваниями, включая СД, имеют больший риск тяжелой COVID-19 и смертности. Среди случаев смертности от COVID-19 в Ухане (Китай) основными сопутствующими заболеваниями были СД (42,3 %), артериальная гипертензия (53,8 %), заболевания сердца в анамнезе (19,2 %) и церебральные расстройства (15,4 %). Также смертность существенно возрастает (на 6 %) при наличии СД (7,3 %) и других сопутствующих заболеваний, таких как сердечно-сосудистые (10,5 %), хронические заболевания органов дыхания, артериальная гипертензия и рак. По данным исследований, распространенность СД у людей, зараженных вирусом, примерно такая же, как и в общей популяции, даже несколько ниже. Согласно результатам метаанализа 12 исследований, которые описывают данные 2108 китайских пациентов с COVID-19, распространенность СД составила 10,3 %, что было аналогично распространенности 10,9 % в 2013 году. Пациентам с СД рекомендуется придерживаться общих советов по уменьшению риска заражения, а также специфических для лиц с СД. Все современные рекомендации медицинских организаций и научных сообществ подчеркивают важность надлежащего контроля гликемии во время пандемии COVID-19, так как это может помочь уменьшить риск заражения и тяжесть болезни.

Ключевые слова: сахарный диабет; COVID-19