



# Management of diabetes patients during the covid-19 epidemic

Obravnavanje bolnikov s sladkorno boleznijo v času epidemije covida-19

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## Abstract

The year 2020 will undoubtedly be marked by the coronavirus disease 2019 (covid-19) pandemic, caused by the novel coronavirus SARS-CoV-2. It has been shown that in diabetes patients, covid-19 occurs in a more severe form, with these patients being more prone to the need for mechanical ventilation and having higher mortality rates than non-diabetic patients. In the present article, we describe possible pathophysiological mechanisms that could explain a more severe course of covid-19 in diabetes patients. We also describe the recommendations for use and discontinuation of anti-diabetic drugs during infection, and continue by explaining how to adjust the management of this chronic disease during an epidemic. In conclusion, our own experience in organizing outpatient diabetes clinic during the covid-19 epidemic at the University Medical Centre Ljubljana is described. Covid-19 still carries many unknowns, so it will not surprise us, if we soon realize that the findings described so far, are outdated. Nonetheless, the present recommendations for the treatment of diabetes patients during the epidemic will remain in force and will hopefully help to improve and optimize the treatment of our patients, even after the pandemic.

## Izveleček

Leto 2020 bo nedvomno zaznamovano s pandemijo koronavirusne bolezni 2019 (covid-19), ki jo povzročata novi koronavirus SARS-CoV-2. Izkazalo se je, da pri bolnikih s sladkorno boleznijo covid-19 poteka v hujši obliki; v večjem deležu je potrebno mehansko predihavanje, ugotavlja pa se tudi večja smrtnost. V prispevku opisujemo možne patofiziološke mehanizme, ki bi lahko bili povezani s hujšim potekom covida-19 pri bolnikih s sladkorno boleznijo. Navajamo tudi priporočila za uporabo oz. opustitev antidiabetičnih zdravil med okužbo in objavljamo navodila za prilagoditev vodenja te kronične bolezni med epidemijo. Opisujemo lastne izkušnje glede organiziranosti obravnave v diabetološki ambulanti Univerzitetnega kliničnega centra Ljubljana. Pri bolezni covid-19 je še veliko neznan, zato so na tem področju potrebne nadaljnje raziskave. Ne glede na to pa bodo ta priporočila za obravnavo bolnikov s sladkorno boleznijo med epidemijo prispevala k izboljšanju in optimizaciji obravnave bolnikov s sladkorno boleznijo tudi v obdobju, ko bo epidemija minila.

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### Key words:

diabetes; covid-19; SARS-CoV-2; antidiabetic drugs; management of diabetes during epidemic

### Ključne besede:

sladkorna bolezen; covid-19; SARS-CoV-2; antidiabetiki; obravnavanje sladkorne bolezni med epidemijo

Received: 1. 6. 2020

Accepted: 14. 1. 2021



**Cite as/Citirajte kot:** Janić M, Lunder M, Janež A. Management of diabetes patients during the covid-19 epidemic. *Zdrav Vestn.* 2021;90(5–6):322–35.

**DOI:** <https://doi.org/10.6016/ZdravVestn.3093>



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## 1 Introduction

In 2020, the novel coronavirus SARS-CoV-2 spread across the world, causing the COVID-19 pandemic (1). At the time of writing this article, more than 60 million people had been infected and more than 1.4 million people had died, according to the data from the World Health Organization (WHO) (2). COVID-19 is a very transmissible disease, being spread primarily by respiratory secretions, although other routes of transmission cannot be excluded (3). In the majority, it causes mild upper respiratory disease, but a minority of patients develop a moderate or severe lower respiratory disease (pneumonia, acute respiratory distress syndrome – ARDS) or a critical illness with shock and multiorgan failure. Patients with comorbidities such as cardiovascular diseases, arterial hypertension, obesity or diabetes and the elderly are more likely to have a severe course of COVID-19 (1,4,5).

## 2 Diabetes and unfavourable outcome of COVID-19

Diabetes is often associated with increased morbidity and mortality due to pneumonia and influenza, as increased blood glucose levels (> 11 mmol/l) on hospital admission are a predictor of unfavourable outcome (3). This was also true during epidemics of other coronaviruses. During the Severe Acute Respiratory Syndrome (SARS) epidemic, diabetes was an independent prognostic factor of increased mortality, and during the Middle East Respiratory Syndrome (MERS) epidemic, it was also a significant prognostic factor of a severe

disease course and increased mortality. In young patients with pandemic influenza A (H1N1), diabetes was a prognostic factor for ICU admission (1,4,6).

Based on the results of previous studies, it is not entirely clear whether diabetes increases the risk for severe COVID-19, as diabetic patients often have other comorbidities such as cardiovascular diseases, obesity and arterial hypertension, all predictors of unfavourable outcome (3). Despite this, evidence is mounting that diabetic patients have an increased risk for severe COVID-19 and its complications, the need for mechanical ventilation and mortality, similar as with other coronavirus disease epidemics (5,7). Epidemiological studies show that diabetes increases COVID-19 mortality by 50%. A Chinese study with 72,314 COVID-19 patients found a 3-fold increase in mortality in diabetic patients compared to general mortality (7.3% vs. 2.3%), while in Italy, the general mortality was 7.2%; of all that died, 35.5% had diabetes. In these studies, corrections for age and comorbidities were not performed (5,7,8). The findings of a recent French study with 1,317 patients show that in hospitalized COVID-19 diabetic patients, the prognostic factor for disease severity was body mass index (BMI) and not diabetes. During the first hospitalization week, BMI had an independent association with intubation and death (9). There is significantly less data on the mortality rate of patients with type 1 diabetes than with type 2 diabetes. In the aforementioned study, it was shown that patients with type 1 diabetes have a lower risk for an unfavourable

outcome than all diabetic patients, as they are usually younger with fewer comorbidities. However, the number of enrolled patients with type 1 diabetes was small (10). On the other hand, a UK population study showed that patients with type 1 diabetes have increased in-hospital mortality compared to patients with type 2 diabetes after correcting for comorbidities; the odds ratio was 2.86 compared to 1.80 (11). The contributions of diabetes and obesity to unfavourable outcomes of COVID-19 cannot be precisely determined yet. In a Boston study with 178 diabetic patients, it was shown that diabetes is a risk factor for ICU admission, mechanical ventilation and death due to COVID-19, irrespective of the degree of obesity (12). It should also be noted that due to the increased prevalence of type 2 diabetes in the elderly, that could also be a possible reason for the increased prevalence of diabetes in patients with severe COVID-19. In this group, diabetes is also associated with cardiovascular diseases, which also contributes to more severe disease courses (6,13). At the time of writing this article, we are noticing increased mortality of COVID-19 patients in Slovenia. By the end of November, 2020, more than 1,200 people had died, but there is no data yet available on the mortality of COVID-19 diabetic patients (14).

### **3 The pathophysiological association between diabetes and the COVID-19 course**

Diabetic patients have an impaired immune system (both, innate and adaptive) and are at increased risk for infections (15). Diabetes is thought to increase the risk of virus binding

to cells and its entry into cells, reduce virus secretion, and reduce T-cell function and disrupt their ratio. The interferon- $\gamma$  response is impaired, promoting excessive inflammation. Additionally, diabetic patients have pre-existing metabolic characteristics contributing to chronic inflammation. Dysfunctions of the innate and adaptive immune responses contribute to increased excessive inflammation and cytokine storm risk (16). It is clear that comorbidities alone do not explain the increased risk for severe COVID-19 in diabetic patients.

It has also been shown that insulin requirement is significantly increased in patients with severe COVID-19 and diabetes. Insulin requirements are closely linked to inflammatory cytokine concentrations. Several mechanisms have been proposed to explain the effect of the inflammation caused by SARS-CoV-2 on insulin resistance: inflammatory cells reduce skeletal muscle and liver activity and thus inhibit their glucose uptake; additionally, patients with severe COVID-19 have muscle weakness and elevated activity of hepatic enzymes, which speaks in favour of multiorgan failure during a cytokine storm. Thus, insulin requirements have been shown to be disproportionately higher compared to similar critical conditions in other diseases (1,4,6,13,17).

Infection with SARS-CoV-2 is associated with increased activation of the immune and coagulation systems, while diabetes already promotes a proinflammatory and prothrombotic states. In 174 COVID-19 patients in Wuhan, China, diabetic patients had an elevated inflammatory response (higher levels of C-reactive protein (CRP) and interleukin 6, increased

sedimentation rate, neutrophilia and lymphopaenia), increased coagulation rate (increased D-dimer levels), more pronounced metabolic changes (hyperglycaemia, elevated aminotransferases) and more severe forms of pneumonia by radiological standards (1,5,13), therefore increasing mortality. It should be noted, though, that in this study, diabetic patients were older and were more likely to have cardiovascular diseases (1,13).

In COVID-19, viral entry into the target cell is mediated through the endocrine pathway, which plays a role in regulating blood pressure, metabolism and inflammation. The angiotensin-converting enzyme 2 (ACE2) serves as the main entry point into cells for SARS-CoV-2. The enzyme is located in the upper airways, lungs, renal tubules, endothelium, heart, intestines and pancreas. It enables the conversion of angiotensin I and II into angiotensin-(1-9) and angiotensin-(1-7), with the latter having a protective role as a vasodilator, acting also anti-inflammatory and cardioprotective. In COVID-19, it plays an important anti-inflammatory and antioxidant role in the lungs against ARDS. The latter was proved in patients with bird flu (H5N1). The angiotensin-converting enzyme 1 (ACE1) enables the conversion of angiotensin I to angiotensin II, which has vasoconstrictor and pro-inflammatory effects. By binding to ACE2, SARS-CoV-2 reduces the number of ACE2 receptors and by entering into cells, it damages them and accelerates the inflammatory response. In patients with respiratory failure, increased ACE1/ACE2 ratio was observed in the lungs. By reducing the proportion of the otherwise protective ACE2, angiotensin II concentrations

rise, leading to lung injury. Opinions differ on the role of diabetes in ACE2 expression. According to some data, pneumocyte expression of ACE2 rises in diabetic patients, facilitating viral entry into cells. On the other hand, some data show that in these patients, ACE2 is glycolyzed, preventing the formation of metabolic products by the enzyme, and increasing the risk of ARDS (4,5,13,18,19). ACE2 is also present in endothelium, and by binding with SARS-CoV-2 in the vasculature, destruction and death of endothelial cells occurs. This leads to organ ischaemia, tissue oedema and a prothrombotic state, as prothrombotic molecules are released, in addition to endothelial dysfunction. Concomitant diabetes causes endothelial dysfunction by itself, which leads to the summation of both disease states, leading to more severe systemic organ failure and thrombotic complications (16,17).

In diabetic patients, alveolar dysfunction additionally affects the more severe disease course. It has been shown that diabetic patients have pre-existing pulmonary dysfunction. The level of dysfunction corresponds to glycaemic control. The described pulmonary dysfunction in combination with COVID-19 thus contribute to a higher rate of pulmonary complications (16).

The expression of ACE2 on pancreatic  $\beta$ -cells in COVID-19 directly harms the cells, as proven by nonclinical studies. From this, we can deduce that infection with SARS-CoV-2 can lead to *de novo* diabetes development or deterioration of glycaemic control in previously established diabetes. There are few data on *de novo* diabetes in COVID-19 patients. A series of 29 to 184 patients without previously

known diabetes, of whom some had normal HbA1c at admission, found that some developed diabetes during COVID-19 (20). Therefore, patients without known diabetes but with features of metabolic syndrome need testing for diabetes after COVID-19. It should be noted that a significant proportion of patients with type 2 diabetes are not yet recognized and it is possible that diabetes is only detected or confirmed at the time of infection (1,4,6,13,17).

$\beta$ -cell dysfunction may also be the cause of more frequent diabetic ketoacidosis, which is usually associated with type 1 diabetes. However, one of the meta-analyses showed that the majority (77%) of ketoacidosis occurs in patients with type 2 diabetes. This is probably the consequence of direct destruction of viable pancreatic cells in infection with SARS-CoV-2. Only 10% of ketoacidosis occurred in *de novo* diabetes. There are few reports of diabetic ketoacidosis in patients with COVID-19, but all suggest a worse outcome, if it occurs at disease onset or during treatment (21).

Although ACE2 has similar characteristics as ACE1, it is not inhibited by ACE inhibitors. They and angiotensin receptor blockers (ARBs) increase ACE2 expression. Therefore, it has been hypothesized that the use of these drugs, which are often prescribed for diabetic patients due to their protective effects on the heart and kidneys, is associated with easier viral entry into cells and SARS-CoV-2 infection, which would therefore be more severe. On the other hand, increased ACE2 expression could lead to increased proportion of angiotensin-(1-7), contributing to an anti-inflammatory response. Lower angiotensin II

concentrations due to ACE inhibition should additionally strengthen the protective response. Therefore, the association with the use of these drugs and increased mortality or more severe courses of COVID-19, is not clear. Authorities in this field recommend continuing treatment with these drug groups, and similarly for statins as they have proven effectiveness in reducing the inflammatory response in flu and bacterial infections. The use of statins in COVID-19 remains controversial. The results of Chinese studies show that statin use reduces overall mortality and improves healing in COVID-19 patients, while the results of a French study show the opposite – increased mortality of patients with type 2 diabetes hospitalized with COVID-19. Nevertheless, current recommendations advise against statin discontinuation due to the lack of randomized controlled trials on the use of statins in diabetic patients and COVID-19 (4,17,22,23).

An additional mechanism that could explain the link between COVID-19 and diabetes is via the dipeptidyl peptidase 4 (DPP-4) enzyme, a common therapeutic target in type 2 diabetes. In cell studies, DPP-4 was shown to be a functional receptor for the MERS-causing coronavirus. It is not yet clear if a similar mechanism plays a role in COVID-19 pathogenesis. It is, therefore, not clear if DPP-4 inhibitors play an important role in COVID-19 (4,24).

#### 4 Antidiabetic drugs in COVID-19

In mild COVID-19, it is possible to continue with previously established antidiabetic treatment. In patients with

type 2 diabetes and severe COVID-19, most of the oral antidiabetic drugs should be temporarily discontinued. In order to ensure good glycaemic control, insulin may need to be administered, most commonly in the form of subcutaneous injections. In case of high insulin requirements due to the previously mentioned severe insulin resistance, intravenous insulin is recommended. However, treatment with DPP-4 inhibitors in COVID-19 may continue regardless of disease severity, as these drugs, at least according to some studies, may have a protective effect on the disease course (1,3).

#### 4.1 Metformin

Metformin should be temporarily discontinued in patients with type 1 or type 2 diabetes, in particular in states of tissue hypoxia, due to the risk of lactic acidosis (1,25). It should also be temporarily discontinued in haemodynamic instability or severe disease (26). Monitoring of renal function is required, as acute infections increase the risk for acute deterioration of chronic kidney disease or acute kidney injury (1,25). Metformin has been shown to have anti-inflammatory activity in patients with type 2 diabetes (27). It also has immunomodulatory activity via protein kinase inhibition, which has been shown to be protective in murine pneumonia models. It is also protective in chronic respiratory diseases with a reduction in mortality of such patients treated with metformin (13).

#### 4.2 Sulphonylureas

Due to the high risk of hypoglycaemia in the treatment of type 2 diabetes with sulphonylureas, it is

recommended to temporarily discontinue them in COVID-19 when regular meals are not possible, or the patient is haemodynamically unstable. The risk of hypoglycaemia is additionally increased with concomitant hydroxychloroquine treatment, a drug once used to treat COVID-19 (26).

#### 4.3 Sodium-glucose transport protein 2 (SGLT-2) inhibitors

Temporary discontinuation of SGLT-2 inhibitors is recommended in COVID-19 patients with type 2 diabetes due to risk of dehydration and diabetic ketoacidosis, either euglycaemic or hyperglycaemic (1,26). Additionally, proper perineal hygiene is more difficult to ensure during the disease course (27). As with metformin treatment, monitoring of renal function is recommended due to the risk of acute kidney injury (1,26).

#### 4.4 GLP-1 receptor agonists

Adequate hydration and regular meals are recommended when treating type 2 diabetes with GLP-1 receptor agonists (1). In mild COVID-19, continuation of treatment with GLP-1 receptor agonists is recommended. In severe disease and haemodynamic instability, temporary discontinuation is recommended, among other things due to impaired subcutaneous absorption (26). It should be remembered that many patients with type 2 diabetes receive long-acting (weekly) GLP-1 receptor agonists. Their effects can still be present upon hospital admission but usually cease after 7 days since the last application, manifesting in a gradual rise in glycaemia. It is then necessary to either continue treatment with a new

injection of the same drug or modify antidiabetic treatment. GLP-1 receptor agonists have an anti-inflammatory effect in patients with type 2 diabetes and in some nonclinical models, they are also thought to act protectively in the event of lung injury (27).

#### 4.5 DPP-4 inhibitors

Continuation of treatment with DPP-4 inhibitors is recommended in COVID-19 patients with type 2 diabetes (1). They present little risk for hypoglycaemia, making them particularly safe (26). Treatment with DPP-4 inhibitors can continue even in the critically ill and with concomitant insulin to achieve better glycaemic control (26).

#### 4.6 Insulin

Continuation of insulin treatment is required in COVID-19 patients with type 1 and type 2 diabetes. More frequent monitoring of blood glucose (every 2–4 hours) is recommended with insulin dose adjustments as required. Glycaemic targets depend on the individual's age, comorbidities and diabetes type (1). Insulin is safe and the treatment of choice in the critically ill (3,26).

### 5 Diabetes management during the COVID-19 epidemic

During the COVID-19 epidemic, good diabetes management is crucial (Figure 1), enabling adequate immune system functioning and reducing the risk of infection or its severe course (3). In case of deterioration of glycaemic control, a consultation

with a diabetologist or treating specialist through the telemedicine system or via remote contact is required. Frequent monitoring of capillary glucose is important, or even better, continuous glucose monitoring, offering the most accurate insight into the glycaemic status. It provides the patient, relatives and treating specialist with a good insight into the glycaemic status, enabling changes of antidiabetic treatment (26).

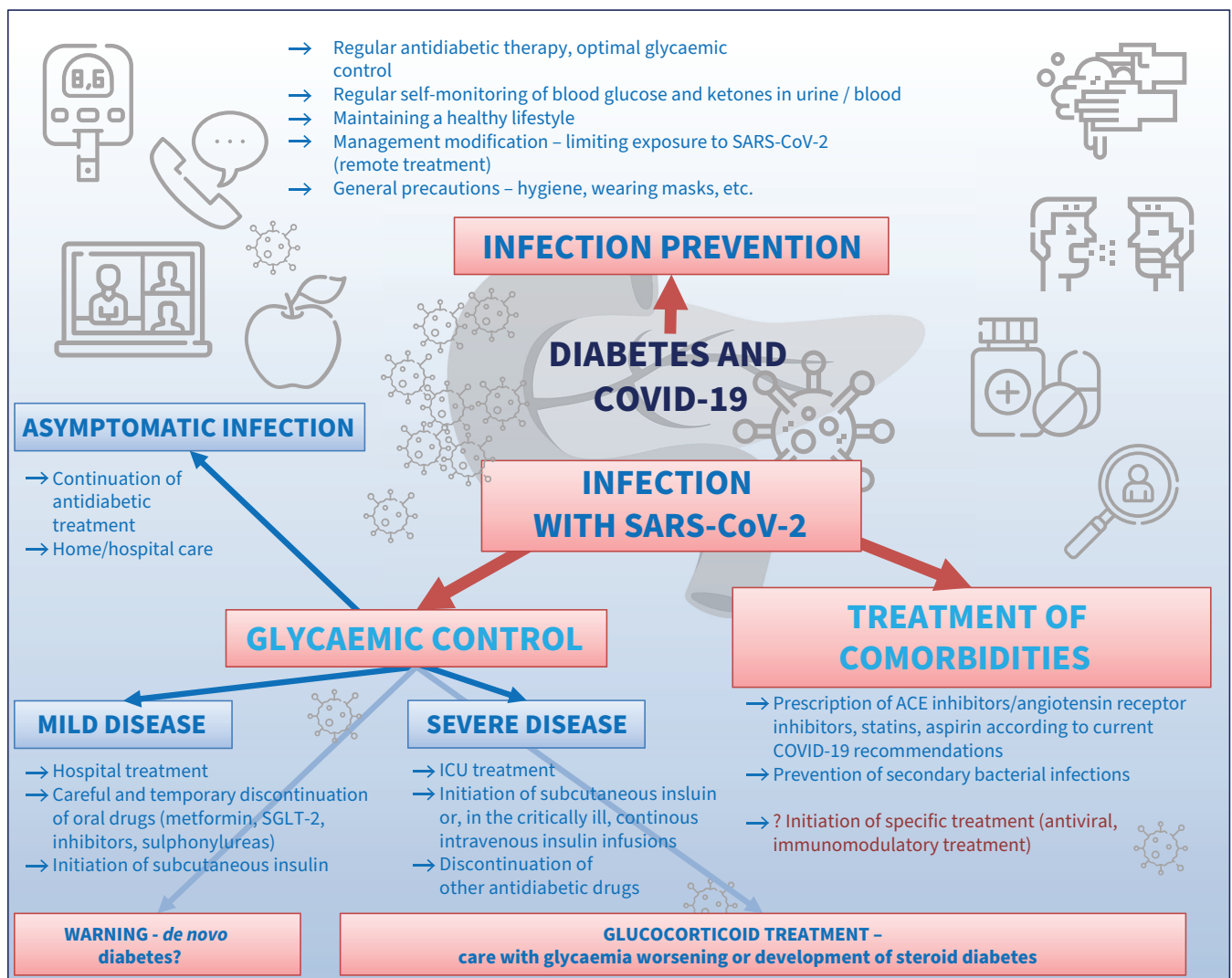
In mild disease and with patients able to eat satisfactorily, continuation of antidiabetic treatment is possible. If possible, more frequent blood glucose monitoring and dose adjustments are needed. In severe disease, treatment modifications are required. Treatment decisions are based on several factors, particularly haemodynamic stability, glycaemic profile, nutritional status, renal function, hypoglycaemia risk, drug interactions and availability of antidiabetic medication (3,26). Upon hospitalization, subcutaneous multiple daily injections of insulin is recommended for non-critically ill diabetic patients. In critically ill patients, continuous intravenous insulin infusion is recommended, while subcutaneous insulin is not recommended nor suitable (as previously described) (1).

As part of severe or critical COVID-19 (ARDS, multiorgan failure, etc.) treatment, patients often receive high-dose glucocorticoids (28,29), which can lead to hyperglycaemia with pre-existing diabetes or the development of steroid diabetes (in 20–54% of patients). Insulin treatment is most often required in COVID-19 patients whose diabetes develops or deteriorates with glucocorticoid treatment, usually with subcutaneous injections,

or in cases of severe hyperglycaemia and the critically ill, with continuous intravenous insulin infusions. In case of a small increase in glycaemia during treatment with glucocorticoids, the introduction of oral antidiabetic drugs, such as sulphonylureas or glinides, is also possible. A prerequisite for the latter, of course, is that the patient is capable of oral food intake (30).

Special attention must be paid to patients with type 1 diabetes.

Continuation of intensified insulin treatment with regular monitoring of blood glucose and ketones in urine or blood is recommended (26). Such patients in particular require good glycaemic control to prevent metabolic deterioration and diabetic ketoacidosis. To educate patients on the meaning of these complications and their detection, the importance of measuring ketones in urine or blood is emphasized. With positive values, a consultation



**Figure 1:** Demonstration of SARS-CoV-2 infection prevention in diabetic patients and measures for glycaemic control according to different levels of patient involvement and treatment of comorbidities with COVID-19.

Legend: ICU - Intensive Care Unit.



with a physician is recommended (1).

The type 1 and type 2 diabetes treatment goals during COVID-19 are: plasma glucose concentrations between 4 and 8 mmol/L and HbA1c below 7% (1). In the critically ill and patients with multiple comorbidities, higher glycaemic targets are allowed (above 10 mmol/L) (26). Target values with continuous glucose monitoring is Time in Range (TIR) (between 3.9 and 10.0 mmol/L) of more than 70% for the majority of patients or more than 50% in the elderly, frail and patients with multiple comorbidities. Time in the hypoglycaemic range (below 3.9 mmol/L) should be below 4% or less than 1% in the elderly or particularly frail patients (1).

Diabetic patients often have other comorbidities, such as arterial hypertension and hyperlipidaemia. It is important to continue with treatment of comorbidities during COVID-19 and that drugs are not discontinued. Most patients with type 2 diabetes are overweight or obese, which becomes problematic if intubation or mechanical ventilation are required, as this is more difficult in these patients. Therefore, overweight and obese diabetic patients are at increased risk for complications of mechanical ventilation and unfavourable COVID-19 outcomes (1).

Routine clinic and hospital-based management of diabetic patients is not recommended during the epidemic, unless absolutely necessary. The spread of disease in the population and among at-risk diabetic patients is thus limited. Remote treatment is recommended, either by telephone, e-mail or telemedicine (26). If possible, interpersonal contacts should be avoided to reduce the exposure of critical groups to SARS-CoV-2. Strict adherence to the

rules of social distancing is particularly recommended for diabetic patients (1). Postponement of non-urgent and screening appointments (retinopathy and foot screening) is recommended. In any case, with vision or diabetic retinopathy deterioration or development of ulcers, patients should be treated immediately in the safest possible environment (26).

During the COVID-19 epidemic, non-pharmacological treatment (healthy and nutritious diet, regular exercise) and good cooperation in diabetes treatment are crucial (26,31).

The following are instructions for diabetic patients during the COVID-19 epidemic:

- Just as for the general population, general preventative measures are important: proper hand hygiene, cough and respiratory hygiene, avoiding the infected people, wearing face masks and avoiding travel to areas with high disease prevalence (3,31).
- Adequate nutritional and caloric intake is important (healthy food, based on protein and fibre, with limited intake of saturated fats) (13). Maintaining a healthy diet during the COVID-19 epidemic may be affected by reduced nutrient availability, and in addition, due to a disrupted supply of fresh fruit and vegetables, patients may resort to calorie-rich and less healthy foods (25). With vitamin and mineral deficiency, replacement and supplementation are required (3).
- Regular physical activity is important (13). If outside activities, including group activities, are not possible due to enforced isolation, physical activity at home is recommended (indoor cycling, track running,

stationary aerobic exercises, weight-lifting, etc.) (25).

- Continuation of antidiabetic treatment is important (oral or subcutaneous injections) (13). Ordering and delivering drugs online is advised. It is also important that diabetic patients keep adequate stores of antidiabetic drugs, supplies and devices at home (26).
- Remote or telemedicine consultations with a therapist are recommended (13).
- Regular self-checks and foot care is required to avoid complications, such as diabetic foot. In the event of new foot lesions, an immediate consultation with a physician for instructions or an appointment is required (3).
- In case of sudden new symptoms and signs, such as vomiting, severe shortness of breath, chest pain, limb weakness, etc., the patient should seek immediate medical attention (13). As stress can be associated with hyperglycaemia, diabetic patients are advised to avoid daily news during the epidemic which could lead to increased stress exposure and thus stress hyperglycaemia and anxiety (26).

Last but not least, vaccination against influenza and pneumococcus are recommended in diabetic patients even during the COVID-19 epidemic. The latter in particular is capable of preventing secondary respiratory infections in viral diseases (3).

## 6 Feet and COVID-19

Infection with SARS-CoV-2 can affect the foot, which can be particularly problematic in diabetic patients and

pre-existent diabetic foot. Various skin lesions can appear, such as petechiae, erythema, frostbite-like lesions or ischaemic changes. Foot or hand gangrene can appear, in particular in the critically ill; these changes were termed “COVID toes” (32). In the clinical case of a Spanish woman, feet lesions appeared a few days before the symptoms and signs of COVID-19. Erythema and frostbite-like changes appeared on the toes bilaterally with concomitant neuropathic foot pain which worsened at night and made it difficult to walk. As COVID-19 symptoms and signs subsided, so did these problems (32).

Hypothetically, COVID-19-activated cytokine inflammatory response may lead to deterioration or faster progression of diabetic neuropathy, possibly even Charcot osteoarthropathy. On the other hand, resting while ill may positively affect foot ulceration healing as the foot is relieved by rest (33).

During the epidemic, regular diabetic foot care (hyperkeratosis removal, nail trimming) is difficult due to the limited access to diabetes clinics, regular foot care and pedicure. The latter can lead to exacerbations such as increased hyperkeratosis formation, ulceration, ingrown toenails, and long nail pressures on the surrounding skin, which can lead to ulceration

## 7 Diabetes outpatient clinic organization at the University Medical Centre Ljubljana during the epidemic

During the COVID-19 epidemic, the organization of the work of the diabetes outpatient clinic at the University Medical Centre Ljubljana

was modified. During a rise in infections in March 2020, based on the recommendations from the Ministry of Health (MZ) and National Institute of Public Health (NIJZ), we only saw patients with “urgent” or “very fast” referrals. They were managed at the emergency and triage diabetes outpatient clinic. Management of gestational diabetes and diabetic foot patients was unaffected. Additionally, emergency education and the introduction of insulin took place in an individual form. Patients with gestational diabetes who were unable or unwilling to come in person to the outpatient clinic due to personal reasons were managed by telephone or e-mail, according to their preferences. During the epidemic, the timing of appointments was arranged so that patients had as little contact with other patients as possible in the outpatient clinic. Before they entered the clinic, we asked them about their health, as per NIJZ instructions. In case of symptoms or signs of respiratory infection, we postponed the appointment for 14 days or until clinical improvement. Before entering the clinic, patients disinfected their hands and were given a face mask to wear at all times during the clinic visit. An appropriate distance of at least two metres between patients and staff was enforced. Healthcare professionals wore surgical masks throughout their time in the clinic. After each appointment, a healthcare professional disinfected the table, chair and door handle and ventilated the room. Healthcare professionals also practised regular hand disinfection.

In times of increasing numbers of infections during the epidemic, we

did not see patients with “fast” and “regular” referrals, in accordance with MZ and NIJZ instructions. In case of problems, patients consulted with healthcare professionals via the telephone or e-mail. If remote management proved inadequate, patients were invited to the outpatient clinic. During the COVID-19 epidemic, the diabetes clinic telephone line was open throughout the working day, not only during office hours. In addition, in order to facilitate informing patients about the changed work regime in the diabetes clinic, we also prepared and regularly updated information on the clinic’s website. In accordance with MZ and NIJZ recommendations, screening appointments (retinopathy and foot screening) were cancelled during the epidemic. We resumed seeing patients with “fast” and “regular” referrals at the end of April 2020, once daily infections started falling. We took into account the NIJZ security recommendations. Before entering the clinic, patients filled in a health questionnaire; we only saw patients in the clinic if their health allowed it, otherwise the patient received a new appointment date. A new form of telemedicine service is currently being established with the cooperation of the University Medical Centre Ljubljana telemedicine team. In addition to enabling an up-to-date insight into the glycaemic status with the possibility of warnings with the help of individually preset alarms, the latter will enable rapid action by the healthcare professional as well as easy communication between the patient and the physician or the telemedicine team after a video call via a telemedicine application.

## 8 Conclusion

According to data from studies, diabetic patients are at increased risk for severe COVID-19 and increased mortality. Therefore, self-isolation and good glycaemic control are crucial for them. In severe disease, temporary discontinuation of some anti-diabetic drugs, such as metformin and SGLT-2 inhibitors, is recommended; care must be taken with sulphonylureas and GLP-1 receptor agonists. In critical disease, insulin treatment should be initiated at least temporarily. Particular attention must be paid to patients with type 1 diabetes, in whom more frequent monitoring of blood glucose and ketones in urine or blood is recommended. Treatment of

comorbidities such as arterial hypertension and hyperlipidaemia should continue. Management and control appointments in diabetes outpatient clinics need to be modified to avoid unnecessary contacts between patients. According to the data from studies, precise mechanisms and the relationship between diabetes and COVID-19 still remain unexplained. New research is needed to shed light on these mechanisms and to open up new ways of managing and treating this very vulnerable group of patients. Until then, or until vaccines and effective drugs become available, generally accepted recommendations on hygiene measures remain in place, with additional emphasis on the crucial importance of glycaemic control.

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