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Diabetes and COVID-19

Disease—Management—People

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Summary The current pandemic of SARS-CoV-2 coronavirus disease 2019 (COVID-19) is a particular challenge for diabetes patients. Diabetes mellitus predisposes to a particularly severe course of the disease and doubles the COVID-19 mortality risk due to pulmonary and cardiac involvement. In addition, diabetes patients often suffer from comorbidities which further worsen clinical outcomes. Glycemic control during infectious diseases is often suboptimal, and antidiabetic drugs and insulin therapy have to be adapted accordingly. On the other hand, access of diabetes patients to outpatient clinics are limited during the ongoing season urging alternative treatment options, particularly the implementation of novel telemedicine strategies. Hence, the opportunity of the COVID 19 crisis should be taken to make a significant step forward in the care for diabetes patients.

Keywords Viral pneumonia · SARS-CoV2 · Diabetes complications · Diabetes therapy · Telemedicine

SARS-CoV-2 infection and its relation to diabetes

Coronavirus disease 2019 (COVID-19) is an infectious and communicable respiratory disease caused by the recently surfaced betacoronavirus severe respiratory coronavirus syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 pandemic exerts a major and universal impact on the human population. Although the case fatality rates of previous coronaviruses middle eastern respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV (35% and 11%) were considerably higher than with SARS-CoV-2 (around 2%), SARS-CoV-2 has been transmitted much more rapidly and could not be confined to certain regions resulting in a quickly evolving pandemic [1]. As of 6 April 2020, 1,309,439 people worldwide have been tested positive for SARS-CoV-2 and 72,638 died from COVID-19 [2]. On the same day, 12,206 persons were tested positive and 220 fatalities were noted in Austria [3]. Moreover, 1074 COVID patients were hospitalized, 250 in intensive care units [4] with most being invasively ventilated.

Both SARS and SARS-CoV2 enter the body through angiotensin converting enzyme 2 (ACE2), while MERS uses dipeptidyl peptidase-IV (DPP4) as its receptor [5, 6]. Both enzyme expression patterns change in diabetes, albeit in different ways, making the receptor proteins themselves an unlikely explanation for the elevated risk [7, 8]. Instead, research focus is shifting more towards impairment of immune response in diabetes as a cause for risk elevation [9, 10].

Diabetes and SARS-CoV-2 susceptibility

The first few published case series have described diabetes, among other commonly related diseases, such as arterial hypertension, obesity and coronary heart disease, to be a risk factor either for COVID-19 itself or a more severe clinical course and mortality [11–13]. The reason for this remains unclear but the risk population pattern is strikingly similar to the previous fatal coronavirus outbreaks of zoonotic origin, SARS and MERS [14, 15].

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Several investigations have demonstrated a higher susceptibility to some infectious diseases in diabetes patients particularly of bacterial origin, probably owing to a dysregulated immune response [16]. Diabetes patients comprise a significant proportion of hospitalized COVID-19 patients. Across Chinese provinces a diabetes prevalence of 7.4% but even up to 20% was reported in COVID-19 patients [17–22]. In Italy the prevalence of diabetes in hospitalized COVID-19 patients was 8.9% moderately exceeding the local overall diabetes prevalence (6.2%) and roughly reflecting that in people aged 55–75 years [23]. Thus, it appears that diabetes patients exhibit only a slightly elevated susceptibility for SARS-CoV-2 infection.

Diabetes and COVID-19 clinical course

A different picture, however, is seen when diabetes is related to disease severity. A report from China showed that patients with diabetes had a higher prevalence of cardiovascular disease (32.4% vs. 14.6%), and less fever (59.5% vs. 83.2%) compared with patients without diabetes [16]. Notably, diabetes patients presented with higher inflammatory serum markers including lactate dehydrogenase (LDH), c-reactive protein (CRP), ferritin, D-dimer, lower lymphocyte counts, and more pronounced computer tomography (CT) imaging pathologies indicating more severe overall and particularly lung involvement [16]. The D-dimer levels, which are strongly linked to a higher mortality in COVID-19 [24], are significantly higher in patients with diabetes indicating a disposition to a hypercoagulable state [16].

One of the first reports on COVID-19 patients revealed that diabetes patients were at higher risk for need of intensive care, which usually means invasive ventilation. In this report 22.2% of intensive care unit patients had diabetes compared to 10.1% in the overall hospitalized COVID-19 population. Hence, diabetes confers a similar increase as noted for other risk populations such as those with hypertension, or cardiovascular disease [20]. A comprehensive report on 1099 patients in China showed a prevalence of diabetes of 7.4% in the overall COVID-19 population; however, 16.2% in those with severe disease [17]. Moreover, 26.2% of patients experiencing the primary composite end point, i.e. admission to an intensive care unit, the use of mechanical ventilation or death had diabetes, a roughly 3.6-fold enrichment in the critically affected patients. A recent meta-analysis calculated an odds ratio of 2.2 for diabetes patients to be admitted to an intensive care unit [13]. Accordingly, diabetes was significantly associated with the development of acute respiratory distress syndrome (ARDS) with a hazard ratio of 2.3 [25]. In summary, the pooled ratio of diabetes among COVID-19 patients with a more severe course compared to those with the more favorable course was 2.26 indicating a significantly elevated risk [23].

A similar picture evolved when looking at 2,003 COVID-19 fatalities. Prevalence of diabetes was about twofold increased in the non-surviving compared to the surviving COVID-19 population in China and Italy [23, 25]. These data mirror the higher mortality rates of diabetes patients in SARS and MERS [26]. Moreover, presence of diabetic complications potentiates diabetes-related mortality [16]. Of note, plasma glucose levels and diabetes were independent predictors for mortality and morbidity in patients with SARS [16] but are not yet evaluated in the current COVID-19 season. In conclusion, diabetes not so much increases the risk of SARS-CoV-2 infection, but significantly enhances COVID-19 severity and mortality.

The role of acute glycemic control after COVID-19 manifestation on clinical outcomes has not been studied yet; however, in influenza in vitro and animal data suggest that, among other negative effects, hyperglycemia facilitates local viral replication in the lungs and impairs anti-viral immune response [27, 28]. Therefore, acute glycemic management could play an important role in limiting viral replication and disease duration in patients with diabetes.

Cardiac injury, defined as blood levels of cardiac biomarkers (high-sensitivity troponin I) above the 99th percentile upper reference limit, is significantly associated with mortality in COVID-19 patients [29]. Patients with cardiac injury compared to those without had a significantly higher prevalence of diabetes (24.4% vs. 12.0%). Multivariable adjusted Cox proportional hazard regression revealed cardiac injury and ARDS, but not diabetes itself being an independent mortality risk factor. These data indicate that the adverse outcome of diabetes patients is due to a higher rate of cardiac and pulmonary complications [29].

Unfortunately, available data do not differentiate between type 1 and type 2 diabetes in COVID-19, making it difficult to compare the contribution of pre-existing metabolic syndrome, as it occurs in most patients with T2DM, against hyperglycemia without other concomitant metabolic disturbances. Retrospective data about infection rates in diabetes suggest that people with T1DM are at a greater risk for infectious disease in general, with death rates being similar to those with T2DM. Compared to matched control groups people with both diabetes types have significantly increased mortality from infectious diseases[30]; however, data stratified by type of pathogen (e.g. bacterial, viral) are currently not available.

Some viruses might trigger islet autoimmunity and hence diabetes development [31]. Exploring data on COVID-19 patients with diabetes showed that 29.2% were under insulin therapy on admission and an additional 37.5% received insulin therapy after admission, indicating poor glycemic control during the disease [16]. An earlier study of SARS found higher fasting blood glucose levels even in absence of severe disease and glucocorticoid therapy [32]. Moreover, a strong immunostaining of SARS-CoV and even more SARS-

CoV-2 receptor ACE2 in Langerhans islets suggests potential direct damage to insulin-secreting cells by SARS corona viruses [33].

Chronic subclinical inflammation in diabetes is part of a disturbed immune response. In SARS-CoV-2 infection, a cytokine storm occurs in severe disease as indicated, e.g. by elevated interleukin (IL)-6 serum levels [34], which are higher in diabetes patients along with enhanced disease severity indicating a more pronounced cytokine storm [16]; however, it is unknown whether treatment with IL-6 blockade has a beneficial effect on the outcome of COVID-19 in patients with diabetes [35].

Impact of COVID-19 on diabetes complications

The COVID-19 pandemic is driving significant changes in the healthcare system and disrupting current best practices for diabetic limb preservation, leaving large numbers of patients without care [36]. The impact of COVID-19 on diabetes complications is difficult to quantify, since data are lacking from the ongoing season; however, one analysis from a cardiac catheter laboratory implied that there is a significant delay in time from onset of STEMI symptoms to coronary intervention compared to the previous year, most notably in time to first medical contact [37].

Another potential complication particularly vulnerable to disruptions in healthcare provision is limb preservation in patients with chronic wounds and peripheral arterial disease as there are very few substitutional options for direct specialist contact. Some authors make a case for triage systems which enable reduction of in-hospital visits for nonlife-threatening wounds, allocating patients with less severe problems to office visits or even telemedical care and remote monitoring [36]. While not yet a validated approach, this could free up valuable resources in hospitals for those with urgent treatment indications.

Data on acute complications during pandemic-related healthcare crises (e.g. diabetic ketoacidosis, hypoglycemia) almost do not exist, but will hopefully be generated in the aftermath of SARS-CoV-2, as this may allow planning in comparable future events. In a case series 10.3% (3/29) of the patients suffered at least one episode of hypoglycemia (<70 mg/dl, i.e. <3.9 mmol/l) [38]. Aside from seeking to achieve individual glucose and other metabolic targets there are currently no special recommendations for people with diabetes regarding COVID-19 and its complications [39].

Diabetes treatment during COVID-19

The initial impact of COVID-19 on glycemic control seems to be akin to other infectious disease states: acute inflammatory response leads to insulin resistance and subsequent hyperglycemia which in turn necessitates intensification of pre-existing diabetes therapy [40]. In a retrospective study from Wuhan, China, 56% out of 881 blood glucose measurements in hospitalized patients with COVID-19 were abnormal [38]. This illustrates the necessity for a proactive approach in diabetes care for these patients, despite blood sugar not being the main focus. Moreover, approximately 70% of patients with T2DM either had to start or intensify insulin therapy during the course of hospital admission [16].

Regarding optimal treatment for COVID-19 patients with diabetes, physicians should refer to the 2019 guidelines from the Austrian Diabetes Society (Österreichische Diabetes Gesellschaft, ÖDG). Insufficient glycemic control has been shown to negatively affect outcomes in several diseases, leading to increased length of hospitalization, rate of complications and mortality. Antidiabetic therapy should be initiated or intensified for patients who repeatedly have preprandial blood glucose values of >180 mg/dl (>10 mmol/dl). Target glucose depends on several patient factors, particularly comorbidities, but generally lies between 140 and 180 mg/dl preprandially for those with severe signs of COVID-19. Owing to its well-established efficacy and safety profile insulin is the therapy of choice for these patients, preferably as multiple daily injections or, in intensive care units, continuous intravenous infusion by syringe pump. For dose suggestions respective passages in the ÖDG guidelines are recommended [41].

Concomitant medication should be reviewed in every hospitalized patient on admission. Metformin and sodium glucose transporter (SGLT2-)2 inhibitors, both extensively used in type 2 diabetes, can have grave, potentially life-threatening adverse effects in acute sickness, which is why they should be temporarily discontinued during COVID-19. It might be prudent to withhold ACE inhibitors and angiotensin receptor blockers (ARB) during acute illness due to increased risk of acute kidney injury in selected diabetes patients [42, 43]; however, a general stop of renin-angiotensin-aldosterone inhibitors in COVID-19, based on considerations of their potential to up-regulate the SARS-CoV-2 receptor ACE2, is not recommended [44].

Care for diabetes patients during the COVID-19 pandemic

Physicians treating patients with diabetes outside of the hospital setting should be aware of the impact social distancing and quarantine measures may have on glycemic control. Calling on people to stay at home will most likely reduce the amount of physical exercise compared to usual daily routine. While there are no reliable empirical data on this topic, one can expect that calorie balance will increase during that period in a proportion of subjects. Both aspects may lead to a deterioration in glycemic control. All patients, particularly those with type 1 diabetes, should be advised to increase the frequency of blood glucose measurements. Those with COVID-19 should furthermore be

re-educated in recognition and handling of diabetic ketoacidosis since infection is one of its most frequent triggers [45].

The COVID-19 has also impacted many treatment facilities for patients with diabetes. In order to minimize potential spreading many hospitals have reduced their outpatient clinic capacities to a bare minimum for emergencies. Additionally, many licensed physicians have adopted similar strategies, seeking to minimize direct patient visits to their offices. Depending on the duration of these measures this may leave a huge proportion of diabetes patients in an insecure state, with the inability to get a routine check and no option to intensify a potentially insufficient therapy. Insufficient glucose control has the potential to provoke numerous acute and chronic complications healthcare systems will have to deal with after the COVID-19 pandemic. Telemedicine could be a reasonable approach to at least partly mitigate the problem of uncontrolled diabetes. The more widespread use of flash glucose monitoring (FGM) and continuous glucose monitoring (CGM) enables the physician to get insights into complete daily glucose profiles with minimum time investment from the patient. This approach is especially suitable for experienced type 1 diabetes patients since their insulin dose might be easily adjustable without the need for face to face contact. In type 2 diabetes, however, this option is of limited use as FGM and CGM are not commonly used in this population yet; however, meta-analyses have found that benefits of telemedicine in type 1 and type 2 diabetes are modest and do not affect clinically relevant end points [46–48]; however, telemedicine with improved instruments could complement personal contact in standard diabetes management. Notably, access to insulin, oral antidiabetics and glucose management supplies has not been compromised by the SARS-CoV-2 pandemic as of yet in this region [39].

Conclusion

Diabetes patients are prone to a severe clinical course of COVID-19 and significantly increased mortality. Hence, diabetes patients and particularly those with comorbidities must be urged to comply with social isolation and other preventive measures for COVID-19 infection. Moreover, patients must be made aware of hyperglycemia by stress and infection, and be counselled on how to adapt glucose lowering therapy. Telemedicine methodologies including interdisciplinary counselling with diabetologists, nutritionists and wound managers must be established including compensation models. In addition, data privacy issues occurring with telemedicine must be solved in cooperation with healthcare providers to promote the security of diabetes patients during the pandemic while maintaining optimal glucose control. Moreover, such strategies developed through the restrictions caused by the pandemic crisis have the potential to become novel standards of diabetes treatment in the future. Treatment of diabetic complications particularly foot care has to be delivered under safety conditions in order to prevent later amputations. Moreover, the COVID-19 pandemic should be used to systematically collect data on patients with diabetes in order to learn for future epidemics. Overall, the COVID-19 pandemic crisis should be used to establish innovative management strategies for patients with diabetes.

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