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Diabetes and COVID-19: Short- and Long-Term Consequences

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ABSTRACT

When the corona pandemic commenced more than two years ago, it was quickly recognized that people with metabolic diseases show an augmented risk of severe COVID-19 and an increased mortality compared to people without these comorbidities. Furthermore, an infection with SARS-CoV-2 has been shown to lead to an aggravation of metabolic diseases and in single cases to new-onset metabolic disorders. In addition to the increased risk for people with diabetes in the acute phase of COVID-19, this patient group also seems to be more often affected by long-COVID and to experience more long-term consequences than people without diabetes. The mechanisms behind these discrepancies between people with and without diabetes in relation to COVID-19 are not completely understood yet and will require further research and follow-up studies during the following years. In the current review, we discuss why patients with diabetes have this higher risk of developing severe COVID-19 symptoms not only in the acute phase of the disease but also in relation to long-COVID, vaccine breakthrough infections and re-infections. Furthermore, we discuss the effects of lockdown on glycemic control.

Introduction

Currently (March 2022), more than 450 million people worldwide were confirmed to be infected with SARS-CoV-2 and more than 6 million individuals had died due to COVID-19. After the onset of the pandemic, it was rapidly recognized that people with comorbidities and in particular metabolic diseases have a higher risk of developing severe COVID-19 and display an increased mortality [1]. Furthermore, it transpired that there are sex-specific differences in relation to COVID-19; severity and mortality is higher in men, whereas the incidence of long-COVID is higher in women (reviewed in [2]). In addition to the acute illness, people with diabetes appeared to be more prone to long-COVID, vaccine breakthrough infections and re-infections. Here, we will discuss this interface between diabetes, COVID-19, and long-COVID (▶ **Fig. 1**).

Diabetes and acute COVID-19

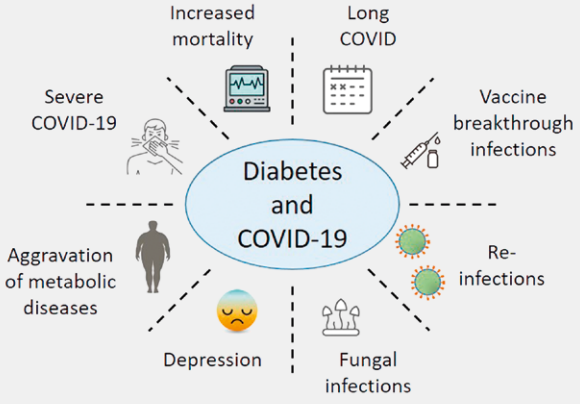
Patients with diabetes frequently exhibit a chronic subclinical low-grade inflammation due to impaired insulin signaling. This leads to a decrease in anti-inflammatory cytokines and to a higher expression of the pro-inflammatory cytokines TNF-α, IL-6 and IL-1β. These cytokines inhibit insulin signaling [3], thus escalating insulin resistance [4]. In severe COVID-19, the inflammatory response to SARS-CoV-2 may promote insulin resistance and endothelial dysfunction [1]. Synergy between COVID-19 and type 2 diabetes mellitus (T2DM) may further amplify this inflammatory response, thereby contributing to critical disease [5]. By triggering airway hyper-reactivity, insulin resistance increases the risk of respiratory failure and cardiopulmonary collapse in patients with diabetes and COVID-19 infection [6].

Patients with COVID-19, without any pre-existing history or diagnosis of diabetes, are reported to have a greater prevalence of hyperglycemia [7]. However, stress hyperglycemia and insulin resistance are also characteristics of other acute critical illnesses [8]. Therefore, it remains unclear whether COVID-19-associated hyperglycemia and insulin resistance is more severe than in non-COVID patients with similar disease severity. As in non-COVID critically ill patients, the ideal blood glucose target remains to be defined as patients with uncontrolled or poorly controlled blood glucose levels were shown to experience a worse disease course than those with normoglycemia [9].

Data have shown that acute COVID-19 in single cases may lead to development of type 1 diabetes mellitus (T1DM), and in many cases an infection with SARS-CoV-2 led to a deterioration of prediabetes or pre-existing T2DM [1]. We and others have shown that pancreatic beta-cells may be directly infected with SARS-CoV-2, which may lead to beta-cell damage and possibly insulin resistance [10–13]. These findings were confirmed in a recent study from the American Centers for Disease Control and Prevention, where the risk for newly diagnosed diabetes in adolescents was estimated to be more than doubled when compared to adolescents without an infection with SARS-CoV-2 or with other respiratory infections [14]. A similar study with 600 055 people showed an increased risk of new-onset T2DM after COVID-19. This risk was higher after moderate/severe COVID-19 than after mild symptoms [15]. Furthermore, the risk was higher than in influenza controls excluding general morbidity after viral illness [15].

In addition to infection-induced hyperglycemia, corticosteroid-induced hyperglycemia is a common medical problem [16], where glucocorticoids lead to an increase in insulin resistance with increased glucose production and inhibition of the production and secretion of insulin in pancreatic beta-cells. This problem is also encountered during the coronavirus pandemic due to long-term treatments with dexamethasone, which may lead to long-lasting metabolic dysregulations [5].

Recently, it was suggested that SARS-CoV-2 might trigger T1DM via post-translational protein modifications and the generation of neoepitopes, which are able to induce islet autoimmunity [17]. This phenomenon is known from other autoimmune conditions, such as rheumatoid arthritis [18] and coeliac disease [19]. Indeed, several antibodies to post-translationally modified islet peptides have been identified [20]. Furthermore, in newly diagnosed patients with T1DM, these antibodies are not only more abundant than those to native insulin [21], they are also more sensitive when compared to standard islet autoantibodies [22]. Therefore, they can also be used as specific biomarkers of disease progression [17].



▶ **Fig. 1** Diabetes and COVID-19: When people with diabetes are infected with SARS-CoV-2, it may lead to a number of short- and long-term consequences.

Diabetes and long-COVID

As the COVID-19 pandemic continues to progress, awareness about its long-term impacts has been growing, and more and more studies dealing with this question are emerging. In long-COVID (also termed post-COVID-19 syndrome or post-acute sequelae), one or more signs or symptoms are persisting over 12 weeks even after the expected period of clinical recovery [23]. According to current knowledge, 10–40 % of people that were infected with SARS-CoV-2 suffer from clinically relevant symptoms of long-COVID [24–26]. These symptoms are experienced 3 to 12 months after recovery from the acute phase of COVID-19 [27]. The main symptoms are difficulties in concentration, cognitive dysfunction, amnesia, depression, fatigue, and anxiety [28–31], and especially older age, female sex, and disease severity were identified as risk factors for persistent neuropsychiatric symptoms [32]. Most of these COVID-19-related persistent symptoms improved over time; however, neurological symptoms seem to last longer than other symptoms [29]. Though to a lesser extent, even people with mild COVID-19

symptoms that were isolated at home often develop long-COVID [24].

Mechanisms explaining the chronic symptoms after COVID-19 are not yet fully understood, and therefore, it is still not possible to foretell the long-term consequences for our health system. In addition to the direct effects of a SARS-CoV-2 infection as mentioned above, it is assumed that the immune response to the virus is partly responsible for the presence of the lasting symptoms, possibly through facilitating an ongoing hyperinflammatory process [33]. Therefore, several hypotheses have been suggested to explain the long-lasting effects of an infection with SARS-CoV-2: 1) Direct infection of the organs during acute infection leading to temporary or permanent damages, 2) virus "left-overs" in tissue reservoirs across the body, which may not be identified by nasopharyngeal swabs, 3) cross reactivity of SARS-CoV-2-specific antibodies with host proteins resulting in autoimmunity, 4) delayed viral clearance due to immune exhaustion resulting in chronic inflammation and impaired tissue repair, 5) mitochondrial dysfunction and impaired immunometabolism, and 6) alterations in the microbiome leading to long-term health consequences [33–36]. In addition to viral effects, the symptoms of long-COVID can be due to effects of hospitalization and drugs, or unrelated to these.

Presence of diabetes may further influence long-COVID via various pathophysiological mechanisms. First investigations have shown that people with metabolic diseases may have a higher risk of developing long-COVID symptoms. Patients with T2DM having a COVID-19 infection had significantly more symptoms of fatigue after the acute illness as compared to those without diabetes [37]. Furthermore, COVID-19 can add to or exacerbate tachycardia, sarcopenia (and muscle fatigue), and microvascular dysfunction in patients with diabetes [38].

As mentioned above, the evidence that SARS-CoV-2 could induce diabetes is growing. However, it is not yet clear whether this might be a fulminant-type diabetes, autoimmune diabetes, or a new-onset transient hyperglycemia [17]. In patients that were hospitalized due to COVID-19, glycemic abnormalities were observed up to 2 months later [7]. However, other long-term studies reported that the prevalence of dysglycemia reverted to pre-admission frequencies in most recovered patients [9].

Antidiabetic medications and COVID-19

An additional compounding issue is the fact that the majority of T2DM patients are taking antidiabetic drugs, which themselves may influence SARS-CoV-2 susceptibility and COVID-19 severity. SARS-CoV-2 replication is initiated by binding of the viral spike (S) protein to the surface receptor ACE2 of the host cell (reviewed in [39]). ACE2 catalyzes conversion of Angiotensin II into Angiotensin 1–7 and represents the vasoprotective, anti-inflammatory and antifibrotic component of the angiotensin renin system [reviewed in [39, 40]). It is still a matter of debate whether upregulation of ACE2 is beneficial for COVID-19 prognosis or not [39]. The effects of antidiabetic medications upon ACE2 expression have recently been summarized [41]. Agonists of "peroxisome proliferator-activated receptor gamma", for example, pioglitazone and rosiglitazone, increase ACE2 gene transcription. In addition, there is indication that pioglitazone can inhibit the secretion of pro-inflammatory cytokines and increase anti-inflammatory ones; it can also attenuate lung injury and reduce lung fibrotic reaction (reviewed in [42]). Metformin, the most frequently employed antidiabetic, reverses lung fibrosis in mouse models [43], which is desirable when treating viral pneumonia. Metformin also preserves the permeability of alveolar capillaries and reduces the severity of ventilator-induced lung injury in rabbits [44]. It reduces pulmonary inflammation and fibrosis in a rat model [45], thereby prolonging survival and attenuating pulmonary injury. Clinical studies indicate that metformin users have a reduced probability to develop COVID-19 [46] and a lower disease mortality [47–50]. DPP4 inhibitors (gliptins), in addition to their antidiabetic actions, have anti-inflammatory effects, reduce cytokine overproduction, and have been suggested as treatment of COVID-19 [51]. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are antidiabetic drugs with numerous pleiotropic and positive clinical effects and have been shown to reduce the risk of cardiovascular death in patients with heart failure regardless of diabetes mellitus status [52]. More recent studies highlight some novel anti-inflammatory activity of SGLT-2 inhibitors which may help reduce excessive cytokine production and inflammatory responses associated with a COVID-19 infection [53].

Other long-term complications of COVID-19 and diabetes

Recovering COVID-19 patients, especially in India, are increasingly reported to contract fungal infections [54]. Mucormycosis, also known as "black fungus", is a serious and potentially fatal fungal infection caused by a rare fungal pathogen mucormycetes. The environmentally ubiquitous fungi, although usually innocuous, may become life threatening in immune-compromised patients. Prior to the corona pandemic, it was estimated that India had a 70–80-fold higher disease burden than any other country in the world though still relatively rare [55]. The time gap between the infection with SARS-CoV-2 and mucormycosis is around 15 days [56–58]. The entry of the fungi usually begins with inhalation of sporangiospores from air/dust through the nasopharynx. Furthermore, contaminated food, cuts/abrasion in the skin, infection from medical devices and the ventilation system may be responsible for an infection [54].

In the first wave of COVID-19, 44 cases and 9 deaths were reported across India in mid-December 2020. However, in the second wave (between April and June 2021) 45 374 cases were reported with a ~50 % mortality rate [59]. Two thirds of these were COVID-19-related and the remaining third was associated with uncontrolled or poorly controlled diabetes or immuno-compromised individuals [60]. While the exact cause of its sharp rise suddenly and specifically during the second wave still remains debatable, it has been observed that people with diabetes who have recovered from COVID-19 infection are more predisposed to mucormycosis. Furthermore, it has been speculated that an indiscriminate use of steroids, antibiotics, and zinc, as a self-medication practice in the COVID-19 pandemic, may have promoted a dysbiosis of the gut microbiome inducing immune-suppression and making the risk groups more susceptible to this fungus [61]. India has the second-largest number of adults with diabetes in the world [59]. Moreover, a high number of people in India do not regularly test their blood sugar levels [62, 63]. Therefore, it is tempting to

believe that uncontrolled and poorly controlled diabetes can be blamed for the emerging epidemic of mucormycosis [59]. An underlying undetected diabetes in COVID-19 patients may result in high sugar levels. Furthermore, in combination with glucocorticoid treatment for COVID-19, this may result in extremely high sugar levels, reaching more than 450–500 mg/dl in patients with diabetes and COVID-19 [64, 65]. This uncontrolled glycemic level impedes the viral clearance and reduces T-cell function by lowering the immune response [66, 67]. In addition, the body cannot utilize this high blood sugar due to limited insulin release, leading to alternative fat metabolism and resulting in ketoacidosis. Thereby, both high sugar and acidic blood generate a flourishing atmosphere for the fungus [68].

Reports suggest that 2–3 weeks of steroid therapy and prolonged ICU stays are enough to weaken the immune system and thereby to increase the susceptibility of patients to mucor infections. The ketoacidosis and ketonemia in COVID-19 patients, also weakens phagocytic activity, and the risk of mucormycosis is further increased [69].

Re-infection and vaccine breakthrough infections

Vaccination against COVID-19 is highly effective in addressing severe COVID-19 [70]. However, currently a high number of SARS-CoV-2 vaccine breakthrough infections and reinfections occur. Obesity and impaired metabolic health are already known to be important risk factors for severe COVID-19. Latest findings indicate that these risk factors might also promote vaccine breakthrough SARS-CoV-2 infections in fully vaccinated people [71]. A recent study including fully vaccinated patients that were admitted to the Yale New Haven Health system hospital concluded that among all pre-existing comorbidities, overweight, T2DM, and cardiovascular disease were frequently seen in patients with severe or critical illness [72]. Another study investigated the effectiveness of COVID-19 vaccination in Scotland's nationwide platform EAVE II. Here, T2DM, coronary heart disease and chronic kidney disease were also associated with increased risk of severe COVID-19 outcomes [73]. These findings confirm previous results from Israel showing that the COVID-19 vaccine effectiveness is slightly lower among people with a higher number of coexisting conditions, such as obesity, T2DM and hypertension, compared with people with a low number of coexisting conditions [70]. Furthermore, these findings are similar to data from patients with obesity and/or T2DM suffering from immunosenescence and increased HbA1c levels, that were demonstrated to exhibit a reduced immune response to an influenza A (H1N1) vaccine [74].

Naturally infected populations are less likely to be re-infected by SARS-CoV-2 than infection-naïve and vaccinated individuals [75]. Although, re-infected individuals suffer from a milder form of the disease, a remarkably high proportion of naturally infected or vaccinated individuals were (re)-infected by new emerging variants. A recent study from Bangladesh showed that at least one of the comorbidities obesity, diabetes, asthma, heart disease, lung disease, and high blood pressure was present in 50 % of all reinfection cases [75].

Lockdown and its effect on diabetes

As hyperglycemia was shown to worsen the COVID-19 prognosis [9], the importance of maintaining a well-controlled blood glucose levels has to be underlined. Around the world, childhood obesity increased during the pandemic. This was due to changes in the daily routines, such as a reduction in physical activity and negative changes in the eating habits during lockdown. This also had negative effects on psychological well-being [76–78]. A meta-analysis investigating the effect of lockdown on glycemic control due to lockdown measures, however, concluded that no significant effects could be observed in HbA1C levels in either T1DM or T2DM. Actually, a reduction in mean glucose and glucose variability in T1DM was observed [79]. These data were confirmed in several other studies around the world [80, 81]. The same conclusion was reached in different studies with children with T1DM, where the glycemic control did not deteriorate under the lockdown [82, 83]. There are even studies showing an improvement in the glycemic control in T1DM children during confinement [84]. These data suggest that it was actually easier for the children and their parents to follow a strict daily routine when they were confined to their homes. This shows that the use of real-time continuous glucose monitoring, parental management, and telemedicine can display beneficial effects on T1DM care. This is further confirmed by the fact that a deterioration was mainly observed in pubertal adolescent boys, where reduced meal frequency mainly due to skipping breakfast, reduced physical activity level scores, increased screen time and sleep duration could explain the adverse impact on glycemic control [85].

The COVID-19 pandemic also affects mental health because of lockdown and quarantine measurements [86, 87]. Diabetes has been connected to an increased risk of depression [88–91], and equally, people with depression exhibit a more than 30 % higher risk of developing diabetes than people without depression [92, 93]. The mechanisms behind this relationship are not yet understood, but inflammation and insulin resistance seem to be involved, since both diabetes and depression are associated with a chronic state of systemic low-grade inflammation [94]. Co-occurrence of diabetes and depression may impair the quality of life in patients with diabetes and when self-management becomes more challenging, as during the COVID-19 pandemic, more intensive support may be required [95]. Motivating and persuading patients with diabetes to change lifestyle and to follow their treatment can be a demanding task. If these patients are then also depressed, it may become even more complicated.

Conclusion

In order to further understand the vicious cycle consisting of the communicable COVID-19 pandemic on one hand and the non-communicable metabolic diseases on the other hand, there is an urgent need for investigating the precise reasons and mechanism(s) of the pathogenesis and pathological elements and discover rational preventative/therapeutic solutions.

Current evidence suggests that an infection with SARS-CoV-2 may lead to hyperglycemia, ketoacidosis, and in single cases new-onset T1DM. Furthermore, COVID-19 may lead to aggravation of prediabetes or pre-existing T2DM. Some studies indicate

that these conditions are temporary and will revert to normal after a certain time. However, this is something that will have to be followed closely within the coming years. Furthermore, it is important to be aware of potential metabolic dysfunctions due to treatments with steroids and/or other new drugs such as protease inhibitors. For exploring the role of diabetes in long-COVID, continuous careful observation of symptom improvement and multidisciplinary integrated research on recovered COVID-19 patients are required.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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