**COVID-19 and metabolic disease; update and clinical management**

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**Search strategy and selection criteria**

We searched PubMed and Google Scholar for articles published up to July 27, 2021. Search items included “COVID-19”, “post-COVID”, “long COVID”, “SARS-CoV-2”, “ACE2”, “DPP4”, diabetes”, “metabolic syndrome”, “obesity”, “hyperglycaemia”, “hyperglycemia”, “hypoglycaemia”, “hypoglycemia”, “insulin”, “steroids”, “glucocorticoid”, “dexamethasone”, “complications”, “risk”, “long-term consequences”, and “endocrine system”. The reference list of original articles, narrative reviews, clinical guidelines, position statements, systematic reviews, and meta-analyses was screened for relevant publications. The final reference list was selected based on relevance to the topic of this Review with preference given to the most recent relevant publications.

**Abstract**

Up to 50% of the people who died from COVID-19 suffered from metabolic and vascular disorders. Notably, there are many direct links between COVID-19 and the metabolic and endocrine systems. Thus, patients with metabolic dysfunction (obesity, hypertension, non-alcoholic fatty liver disease, and diabetes) are not only at higher risk of developing severe COVID-19 but infection with SARS-CoV-2 may lead to new-onset diabetes or aggravation of pre-existing metabolic disorders. Now, with more than a year’s experience, we provide an update on the mechanisms on how metabolic and endocrine disorders might predispose patients to develop severe COVID-19. Secondly, we update on practical recommendations and management of both COVID-19 and post-COVID. Finally, we summarise new treatment options related to COVID-19 and metabolic diseases and highlight current challenges.

**Introduction**

SARS-CoV-2 spread rapidly across the globe in early 2020 causing a worldwide pandemic. Although many who are infected show no or mild symptoms, the resulting disease, COVID-19, has a wide range of presentations including severe illness and fatal outcomes. Across the world, the pandemic has had immense financial impact and many people have been seriously affected through redundancy, reduced income, and restricted work and psychosocial life due to lockdown or quarantine regulations. However, in some areas, the pandemic has provided new opportunities for progress related to digitalisation in private and professional lives including medicine and treatment options.

Around one fifth of the global population is affected by one or more chronic disease conditions putting them at increased risk of severe COVID-19 (defined as fever and at least one sign/symptom of respiratory disease AND requirement for hospitalisation) if infected. 1 Underlying conditions were reported in more than 50% of COVID-19 patients and around one-third had multiple comorbidities. 2 Age and comorbidities common in the elderly such as obesity, diabetes, hypertension, and pulmonary, cardiovascular, kidney, and non-alcoholic fatty liver disease are risk factors influencing the progression and prognosis of COVID-19. 3-8 Thereby, the COVID-19 pandemic in conjunction with type 2 diabetes and obesity, both characterised by severe insulin resistance 9, have numerous consequences. As recently reported, BMI is strongly correlated with immune signatures predicting severe COVID-19. 10 Distinct immunological signatures discriminate severe COVID-19 from non-SARS-CoV-2-driven critical pneumonia 10, and the presence of obesity may shift severe manifestations of COVID-19 to younger ages as reported by the John Hopkins University. 11 In addition, the underlying diseases might be aggravated making the patients more prone to serious long-term consequences. 12,13 The severity and mortality associated with these medical conditions showed significant geographic differences. 2 Deprived populations lacking access to health services in normal circumstances are left most vulnerable during times of crisis. 14 Moreover, in lower income countries, a high socioeconomic status is associated with obesity whereas in higher income countries the inverse is the case. 15 In countries with a low rate of obesity, the fatality rates have been lower. 15

Now, more than 1·5 years after the initial infections, it has been confirmed that people with metabolic diseases are not just prone to severe COVID-19, but also have a higher risk post-acute sequelae of COVID-19 and vaccine breakthrough. 16-18

**Metabolic and endocrine pathways linked to SARS-CoV-2**

# Entry of SARS-CoV-2 into cells is mediated via binding of the viral spike glycoproteins to cellular angiotensin-converting enzyme 2 (ACE2). In the renin-angiotensin-aldosterone system (RAAS), ACE2 acts as key regulator controlling the generation of the vasodilating angiotensin-(1-7) [Ang-(1-7)] from Ang II. Furthermore, ACE2 is able to cleave Ang I to Ang-(1-9), which can be further converted to Ang-(1-7) by ACE. ACE2, Ang-(1-7), and its mitochondrial assembly (Mas) receptor constitute the vasoprotective arm of the RAAS leading to anti-inflammatory and anti-fibrotic responses (Fig. 1A). 19 On the other hand, when ACE activity is high and ACE2 is inhibited, Ang II acts via the Ang II receptors AT1R and AT2R to exert pro-inflammatory responses and to stimulate aldosterone production. Thereby, a deregulation of the ACE/ACE2 balance may lead to arterial hypertension accompanied by an exaggerated inflammatory response, which in the absence of adequate intervention, might culminate in end-organ damage. 20

The cellular levels of ACE2 depend on several factors such as other RAAS components, gene polymorphisms, and clinical conditions such as hypertension and vascular diseases. 21 ACE2 is expressed in many tissues and cell types and therefore at the pandemic onset, we speculated that a high ACE2 expression would be responsible for infection with SARS-CoV-2. 22 In the endocrine system, ACE2 is expressed in all organs of the hypothalamus-pituitary-adrenal cortex (HPA) axis 23, whereas in pancreatic islets, contradicting results have been presented. Some reports show no expression of ACE2 in the islets of Langerhans but in pancreatic epithelial cells only 24-26, whereas others do show expression of ACE2 in beta-cells in a subset of COVID-19 patients. 27-29 We ourselves have performed a study on SARS-CoV-2 infection of beta-cells with 11 patients that died due to COVID-19. Here, in comparison to other studies with just 1-3 patients, we observed that only a smaller percentage of the patients actually do express ACE2 in beta-cells indicating that other factors are involved in the infection as well. 30

# Whether the expression of ACE2 observed in some COVID-19 patients was due to the infection, or conversely, that these patients were infected due to the high expression of ACE2 remains uncertain. Expression of ACE2 is increased upon inflammatory stress suggesting an enhancement of the beta-cell sensitivity to SARS-CoV-2 during inflammatory conditions. 27

# Following binding of SARS-CoV-2 to ACE2, the receptor is internalised by the infected cell leading to a distinct downregulation of ACE2. Such downregulation of ACE2 in the intestinal epithelium has been suggested to lead to upregulation of the sodium-glucose-transporter-1 (SGLT1) thereby precipitating hyperglycaemia. 31 Furthermore, the protective arm of the RAAS is potentially removed which might lead to a multiorgan hyperinflammatory response (cytokine storm) (Fig. 1B). Thus, the RAAS and in particular ACE2 seems to pose attractive targets to fight COVID-19. 32 While medications such as ACE inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) could increase ACE2 expression and potentiate SARS-CoV-2 cell entry 33, increased ACE2 production would result in a higher circulating level of soluble ACE2, which neutralises SARS-CoV-2 (Table 1). 34 The use of ACEi/ARBs is higher in COVID-19 patients compared to control patients, which is caused by the higher prevalence of COVID-19 among people with hypertension, cardiovascular and renal diseases. 35-37 Nevertheless, none of the observational studies performed so far show an association between the use of ACEi and ARBs and disease outcome, severity or death. 38 Significant and independent associations between plasmatic aldosterone and C-reactive protein levels and the severity of COVID-19 have been reported. 39 The SARS-CoV-2 spike proteins require two proteolytic processing steps prior to cell entry. These are mediated by host cell proteases such as furin, **transmembrane protease serine subtype 2 (**TMPRSS2**)** and cathepsin L, leading to fusion of the viral envelope and the plasma or endosome membrane of the host (Fig. 1B). 40,41

# New variants of the original SARS-CoV-2 strain being up to 90% more contagious have emerged. 42-44 Three of these variants (alpha (B.1.1.7), beta (B.1.351), and gamma (P.1)) are among others mutated in the receptor binding domain (RBD), whereby the binding affinity to ACE2 is increased. 45 Another lineage, B.1.617.2 (delta), with a higher affinity to ACE 2 due to mutations in the spike protein shows increased transmissibility of the virus. 46 Thus, blocking the interaction between ACE2 and RBD interaction would be an essential approach to inhibit the transmission and infection with SARS‐CoV‐2 41, and the SARS‐CoV‐2 RBD domain should serve as a central target for conceiving anti‐COVID‐19 therapeutic strategies. 47

# Additional factors expressed among others in pancreatic beta-cells were identified to be critical for infection with SARS-CoV-2 (Fig. 1B). 29,30 Neuropilin-1 (NRP1), known to bind furin-cleaved substrates, facilitates SARS-CoV-2 entry and infectivity 48 suggesting that in cells with a low expression of ACE2, virus entry is increased due to promotion of the interaction between SARS-CoV-2 and ACE2 via NRP1. In addition, high-mobility-group-protein B1 (HMBG1), a DNA binding protein regulating chromatin and known to be pro-viral, was shown to regulate the expression of ACE2 and being essential for viral entry. 49 Furthermore, HMGB1 is released from necroptotic cells, and systemic levels of TNF- and IFN- were demonstrated to cause necroptosis in SARS-CoV-2-infected individuals. 50 Along similar lines, the key kinase mediator of necroptosis, receptor-interacting protein kinase 3 (RIPK3), is strongly upregulated in patients with severe COVID-19 51, suggesting a feed-forward loop of cell death and inflammation. 52 In analogy to HMGB1, members of the switching defective/sucrose non-fermenting (SWI/SNF) chromatin-remodelling complex, such as SWI/SNF related, matrix associated, actin dependent regulator of chromatin A4 (SMARCA4), regulate the expression of ACE2 (Fig. 1B). 49 Such alternative factors are potential new therapeutic targets for inhibiting SARS-CoV-2 infection.

# The Middle East respiratory syndrome (MERS)-CoV receptor dipeptidylpeptidase-4 (DPP4) has also been suggested as an alternative receptor for SARS-CoV-2. 53 DPP4 has previously been shown to be expressed by cells of the immune system as well as on epithelial and endothelial cells in pancreas, lung, and kidney 54, and we have shown that DPP4 is expressed in both the exocrine and endocrine pancreas. 30 DPP4 is an aminopeptidase playing a critical role in glucose metabolism and DPP4 inhibitors are widely used for the treatment of type 2 diabetes. 55 First reports did not show clinical evidence that drugs targeting DPP4-related pathways exhibit any benefits or harm in relation to human coronavirus infections. 56 However, a later study with 2·8 million people showed worse outcomes though probably due to confounding by indication. 57 Recent reports suggest a better clinical outcome and a reduced mortality of COVID-19 infected patients with diabetes mellitus receiving DPP4 inhibitors (Table 1). 58,59 These contradictory results from observatory studies draw the attention to the importance of properly designed randomised, double-blind, placebo-controlled clinical trials in order to ascertain a potential benefit.

**How do metabolic and endocrine diseases predispose for severe COVID-19 outcomes?**

Excess adiposity is a risk factor for severe COVID-19 and mortality though a number of mechanisms including increased inflammation, hypercoagulation and mechanical obstruction. 60 One explanation for the predisposition to poor outcomes in severe COVID-19 may be the physical stress on ventilation by obstructing diaphragm excursion. Furthermore, both diabetes and obesity are associated with an increased risk of pulmonary fibrosis, chronic obstructive pulmonary disorder and reduced respiratory function. 61 Obesity, diabetes and hypertension increase the risk of stroke and cardiovascular complications 62, risk factors also observed in severe COVID-19 (Fig. 2). These patients exhibit an exacerbated coagulation response due to overexpression of pro-thrombotic factors such as coagulation factors (II, VII, VIII, IX, XI, and XII), plasminogen activator inhibitor-1 (PAI-1), and von Willebrand factor, which in combination with pre-existing conditions may increase the probability of stroke or pulmonary embolism. 3,63,64

Metabolic dysfunction may lead to a baseline state of chronic inflammation, as pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β are upregulated in adipose tissue of these patients. These cytokines inhibit insulin signalling 65, and in turn the cytokine upregulation results in both paracrine and endocrine effects, which leads to an increase in leptin and plasminogen activator inhibitor-1 and a reduced release of adiponectin. 66 Thereby, metabolic organs such as white adipose tissue, skeletal muscle, liver and pancreas get infiltrated with macrophages and other immune cells (Fig. 2). 67 In diabetes, insulin resistance via the IRS-1/2:PI3:mTORC2 signalling pathway leads to an increased infiltration with especially M1 macrophages in adipose tissue. 68 Obesity is also associated with a high baseline expression of the IL-6 receptor. In contrast to lean individuals, the expression is not downregulated by increased cytokine levels, and therefore it leads to a constant low-grade inflammatory state termed metaflammation. 69 Dysfunction in insulin signalling further contributes to chronic inflammation via activation of c-Jun and NF-κB leading to a decrease in anti-inflammatory cytokines and an increase in TNF-α, IL-6 and IL-1β. This shift from predominantly an anti-inflammatory to a pro-inflammatory profile enhances insulin resistance. 70

Type 2 diabetes is a progressive disease due to insulin resistance together with chronic inflammation and endothelial and beta-cell dysfunction. 71 In severe COVID-19, the inflammatory response to SARS-CoV-2 infection can worsen insulin resistance and endothelial dysfunction (Fig. 2). Synergy between COVID-19 and type 2 diabetes and obesity may further amplify the inflammatory response and downregulate interferon response contributing to a more severe disease in diabetes and obese patients. 12 Dysregulation of the RAAS and down regulation of the expression of ACE2 in conjunction with stress signalling increases insulin resistance. 68 Thus, insulin resistance, by triggering airway hyper-reactivity, increases the risk of respiratory failure and cardiopulmonary collapse in patients with diabetes and COVID-19 infection. 68

In addition to their role in the immune response against viral infection, cytokines activate the HPA axis, resulting in the release of adrenal glucocorticoids. 72 In turn, glucocorticoids produce negative feedback on immune cells to suppress further synthesis and release of cytokines. Thereby, the host receives a partially protective signal against the destructive consequences of an overactive immune response such as tissue damage, autoimmunity, or septic shock. 73,74 Such effects have been clinically reported during dexamethasone administration, which is currently the most effective treatment for severe COVID-19 with pulmonary involvement. 73 Furthermore, inhaled glucocorticoids such as budesonide have recently been shown to reduce the time to partly recovery after early COVID-19. 75 This has led to the widespread use of glucocorticoids to treat patients with moderate to severe but also frequently with mild forms of COVID-19 (Table 1).

Diseases of the HPA-axis are per se not expected to increase the risk for severe COVID-19. However, hormonal replacement therapies or immunosuppression might increase the possibility of an undesirable outcome. Thus, patients with primary or secondary adrenal insufficiency are at increased risk of poor prognosis if the glucocorticoid replacement therapy is not adequately controlled. 76

**A recent prospective study in renal patients showed that full vaccination with the** mRNA-1273 vaccine (Moderna) induced a seroconversion rate of 95% in dialysis patients, whereas it was markedly impaired in kidney transplant recipients (42%). 77 Seroconversion rates were lower in both types of patients vaccinated with the BNT162b2 mRNA vaccine (Pfizer/BioNTech). Furthermore, immunosuppressive drug number and type were major determinants of seroconversion failure in both dialysis and transplant patients suggesting immune monitoring and adaption of vaccination protocols for these patients.

**How does SARS-CoV-2 affect the metabolic and endocrine systems?**

Upon infection with SARS-CoV-2, toll-like receptors 2, 3, and 4 are activated and IL-1β and IL-6 are released. The metaflammation observed in patients with metabolic disorders allows for a hyper-immune response reaching pathogenic levels. This cytokine release provokes fever, systemic inflammation and subsequently, sepsis. 78

Pathohysiologically, endocrine and metabolic organs including the brain, pancreas, skeletal muscle, adipose tissue, and liver may be damaged either directly or indirectly by the viral infection and contribute to the development of new-onset hyperglycaemia or insulin resistance in COVID-19 survivors. SARS-CoV-2 is able to infect and replicate in human cells of the endocrine and exocrine pancreas. 28 Moreover, we have observed infiltration with immune cells and signs of necroptosis in both the exocrine and endocrine pancreata from COVID-19 patients. 30 This may imply that beta-cell infection with SARS-CoV-2 might lead to either direct or indirect impairment of the beta-cells functions causing variable degrees of metabolic dysregulation.

New-onset hyperglycaemia, ketoacidosis, diabetes and severe metabolic complications of pre-existing diabetes have frequently been observed in patients with COVID-19. 79-85 Data from the German Diabetes Prospective Follow-up Registry (DPV) , which is a nationwide registry with a coverage of more than 90% of paediatric patients with type 1 diabetes, have shown a significant increase in diabetic ketoacidosis and severe ketoacidosis at diabetes diagnosis especially in children younger than 6 years during the COVID-19 pandemic. 86 Of note, indirect effects such as changes in parental behaviour and healthcare accessibility may have had an influence as well on the increase in new-onset type 1 diabetes in children. 87 Nevertheless, evidence accumulates reporting COVID-19 as a cause or trigger of new-onset diabetes. 17 Observations of pancreatitis following COVID-19 have also been reported. 88 Anyway, it remains a subject of discussion if COVID-19 can indeed directly or indirectly lead to new-onset diabetes or accelerate pre-existing unrecognised diabetes or prediabetes. 89 Therefore, this is currently being examined in a global registry (<http://covidiab.e-dendrite.com/>). 85 Furthermore, a group of international software developers, data scientists and health professionals have built a non-for-profit graph-database (neo4J - covidgraph.org) to make all COVID19 related information searchable and accessible in one database (https://covidgraph.org).

**What are the implications for medications and therapy?**

Diabetes and obesity are amongst the main risk factors associated with COVID-19 disease morbidity. Reducing the risk factors associated with COVID-19 morbidity would also be a reasonable public health goal (Table 2). Apart from medical considerations, patients with chronic diseases belong to an especially vulnerable group in the pandemic due to reduced access to medical care and personal insecurity in a social environment with increasing false information. In many areas, access to diabetes care was reduced during the pandemic, and additionally patients were reluctant to access medical care because of fear of exposure to infection on medical premises. A global survey of health care professionals reported that management of diabetes and hypertension was very often disrupted during the pandemic. 90 Additional complications have been due to significant reductions of physical activity, associated with weight gain, due to changes in eating habits. A recent study showed that overall physical activity was lower in adults with type 2 diabetes during the pandemic restrictions particularly in women, elderly, obese and those from ethnic minority populations. 91 Nevertheless, this expected negative impact of the lockdown, retrospective analyses have actually not reported a worsening of glucose control due to life style changes. 92

On the other hand, it is evident that an endemic increase in excess weight and obesity in the population suggested to have caused more than a doubling of type 2 diabetes numbers over the last two decades, has now contributed to an excess of deaths due to COVID-19. 93 Therefore, there is an urgent need for expert advocacy for societal changes for prevention of type 2 diabetes and obesity directed at improving the diet and lifestyle of populations. Individually-targeted evidence-based health promotion, weight management, behavioural change and psycho-social support services need vigorous support from those in the front-line. 94

An increase in perceived stress has been shown to be associated with worse glycaemic control and increased COVID-19 risk. 95,96 Strategies to avoid physical inactivity, and reduce stress levels can promote cardiovascular protection and has to be considered during COVID-19 time. Promotion of physical activity is prioritised by public health agencies and incorporated into routine medical care (Table 2), and a home-based training protocol could be an important and effective strategy for populations needing to remain safe and physically active at home. 97 The interlinked patho-mechanisms between metabolic diseases and COVID-19 create the pathophysiological basis for how to treat diabetes along with controlling dysglycaemia. Managing type 2 diabetes should always include a component of reducing or eliminating insulin resistance in these patients as well as reducing hyperglycaemia (Table 2).

In the last year, we have gained substantial insights into the association of glucose-lowering therapies and drug classes and their association with COVID-19 related mortality (Table 3). 68,98 These results indicated that there is no reason to cease anti-diabetic or hypertensive medication during the pandemic. However, as most studies were observational, performed retrospectively, and may have been affected by confounding by indication, proper clinical studies are urgently needed. Until now, only one single randomised double-blind, placebo-controlled trial of a glucose lowering agent in patients hospitalised with COVID-19 and at least one cardiometabolic risk factor has been published (DARE-19). 99 This study, excluding critically ill patients, showed the SGLT2 inhibitor Dapagliflozin was safe and well tolerated but did neither result in a statistically significant risk reduction in organ dysfunction or death, nor in improvement in clinical recovery. 99 Another observatory study using SGLT2 inhibitors in patients with type 2 diabetes and COVID-19 was associated with an 18% reduction in mortality. 68 However, this is likely due to confounding by indication with reduced use in the elderly, particularly those with renal insufficiency and frailty. However, caution should be taken when using these drugs because they require hydration and appropriateness of insulin doses to prevent euglycaemic or hyperglycaemic ketoacidosis (Table 1).

In addition to the findings that Dapagliflozin had no negative effect on pre-disposition for SARS-CoV-2 infection or aggravation of the disease course, there has been suggestions that DPP4 inhibitors and metformin may even exert protective effects against SARS-CoV-2 infection (Table 1). 100,101 A number of multicentre observational studies reported either no or reduced association with the use of DPP-4 inhibitors and COVID-19-related mortality. 102-104 The DPP-4 inhibitors belong to a group of drugs associated with many advantages, even in severe cases of COVID-19 (Table 3). They are well tolerated, can be used dose-adapted even in end stage renal disease (except saxagliptin), and have a low risk of hypoglycaemia. In a recent analysis in the UK, they had a slightly increased mortality in persons above 70 years. 57 However, this was again likely due to confounding by indication.

Metformin seems to be an effective therapy with pleiotropic effects for patients in acute, chronic, and even recovery phases of COVID-19. 105,106 On the other hand, other observational studies showed a marked increase of lactic acidosis in hospitalised patients with diabetes and COVID-19 but without an effect in mortality. 107

The continued use of sulfonylurea in stable patients with COVID-19 without hypoglycaemia risk and who are having regular meals in an ambulatory setting may be justified. 68 GLP-1 receptor agonists have a tendency to be neutral to COVID-19 mortality and should be carefully evaluated in severely ill patients with COVID-19 considering their anorexic effects. However, their potential beneficial effects should also be balanced, as these drugs have anti-inflammatory and lung protection actions and can be valuable weapons to combat COVID-19. 108,109

## A recent large nationally representative, population-based observational study of 2·85 million people with type 2 diabetes presented statistical evidence that patients who were prescribed metformin, SGLT2 inhibitors, and sulfonylureas had a lower mortality risk than those not using these medications. 57 In this cohort, α-glucosidase inhibitors were associated with a 26% increase in COVID-19 mortality but the numbers of COVID-19 related deaths were too small to evaluate. Their use should be very carefully considered. 57 These associations with therapies are likely due to confounding by indication with certain therapies such as DPP4 inhibitors more likely to be used in the elderly, those with kidney disease and frailty.

To reduce cytokine release in moderate to severe COVID-19, IL-6 receptor blockade with tocilizumab is used. 110 This treatment has been reported to yield a positive effect on insulin resistance and insulin sensitivity. 111 However, hyperglycaemia has been shown to impair the effectivity of this medication. 112 This further underlies the importance of glycaemic control in COVID-19 patients.

It is important to differentiate between ongoing diabetes treatment and the situation that arises during acute COVID-19 infection. There is a strong rationale to maintain recommendations to avoid metformin or SGLT2 inhibitors during severe COVID-19 to reduce the risk of lactic acidosis or ketoacidosis associated with these drugs in the presence of severe infection. In severe COVID-19, intravenous insulin treatment is essential to maintain adequate glycaemic control and avoid the development of acidosis; in many cases insulin requirements are extremely high, reflecting the impact of the hyperinflammatory state on insulin resistance. 68 Insulin also acts anti-inflammatory by suppressing oxidative and inflammatory stress. 113 Many patients previously on oral hypoglycaemic agents will require conversion to insulin during the acute stages of COVID-19 and will require ongoing treatment with subcutaneous insulin following discharge. An important consideration in such patients is the need to manage falling insulin requirements during the recovery stage and reduce insulin appropriately to avoid hypoglycaemia.

**Relevance to risk stratifications**

In addition to a potential risk of developing type 1 diabetes 17, impairment of islet function in people with metabolic disorders should be considered after infection with SARS-CoV-2. 5,22,114 Even if there is no extensive destruction of the islets, many patients may have a need for enhanced treatment with insulin to avoid ketoacidosis and hyperglycaemia. This needs to be closely monitored. Patients with obesity will also have an increased insulin requirement due to an impairment in their insulin-secretion and increasing insulin resistance, which may contribute to their increased risk and mortality. Moreover, based on the Recovery Trial 73 nearly all patients with severe COVID-19 are now receiving dexamethasone, a powerful anti-inflammatory glucocorticoid. While dexamethasone inhibits inflammation 115, it is still a matter of debate whether steroid-induced hyperglycaemia increasing the need for insulin therapy shortly (already 4-6 hours after application) is due to impaired insulin secretion and/or worsening on insulin action. 116 On the other hand, patients with type 2 diabetes and COVID-19 under insulin treatment have shown a worse prognosis with higher mortality associated with insulin therapy. 117 This is likely explained by confounding with severity of disease, insulin treatment being a marker for more advanced diabetes. 68 Although insulin treatment in the ICU is not questionable, hyperglycaemia in persons with diabetes admitted to ICU should be handled by intravenous insulin using exact dosing with a perfusion device. Frequent glucose monitoring is mandatory where treatment with glucocorticoids occurs and other anti-inflammatory drugs and prophylactic anti-coagulant therapy should be provided in patients with diabetes and COVID-19. 118 Importantly, on an emergent basis the FDA issued guidance to expand the availability and capability of non-invasive remote monitoring devices during the COVID-19 pandemic (https://www.diabetes.org/newsroom/press-releases/2020/fda-remote-patient-monitoring-cgm). This change was made in an effort to improve the ability of health care providers to monitor their patients while reducing their exposure to SARS-CoV-2. Both hyperglycaemia and hypoglycaemia are associated with poor survival in patients with COVID-19. Fasting blood glucose in COVID-19 patients with or without diabetes at admission was a strong predictor of death among patients directly admitted to the ICU 119, and severe hyperglycaemia after admission was a strong predictor of death among non-ICU patients. 120 Almost 50% of hospitalised COVID-19 patients were shown to be hyperglycaemic and even normoglycaemic patients showed alterations in their glycometabolic control with insulin resistance and an abnormal cytokine profile. 83 Recently, it was found that also less variability in glucose excursions measured as time in range (TIR) is associated with a lower risk of all-cause and CVD mortality among patients with type 2 diabetes. 121 These findings indicate that both acute hyperglycaemia as well as long-term glycaemic control are essential in people with COVID-19 and that short-term glycaemic control might improve the prognosis albeit it is still not established whether acute hyperglycaemia is an etiological factor driving poor prognosis or simply reflects the severity of the disease. 98

**Breakthrough infections and metabolic disease**

Recent results from Israel show that even with a complete vaccination, patients may be infected with certain coronavirus mutants such as the delta variant. 16 Most importantly, those patients that get infected even though they are fully vaccinated and develop severe symptoms of COVID-19 are frequently suffering of co-morbidities such as hypertension (71%), diabetes (48%), congestive heart failure (27%) and chronic kidney disease (24%). 16 Given the fact that again patients with diabetes and metabolic disease seem to be the most vulnerable group and most prone to develop severe symptoms despite vaccination the necessity for adequate control of glycaemia and blood pressure in our elderly population even after a successful vaccination program has to be maintained with high priority (Fig. 3).

**Long-term consequences and post-COVID monitoring**

Evidence from the outbreak of the closely related SARS-CoV-1 in 2002-2003 suggests that there is a likelihood of long-term metabolic sequelae from COVID-19. Long-term metabolic abnormalities have been observed for up to 12 years in survivors of SARS-CoV-1. These abnormalities included dyslipidaemia and cardiovascular disease as well as signs of abnormal glucose metabolism with insulin resistance and hyperglycaemia, and diabetes. 122,123 Furthermore, a chronic post-viral syndrome characterised by chronic fatigue, variable nonspecific myalgia, depression and sleep disorders was observed. 124 Recent reports have emerged describing similar long-term consequences of COVID-19 designated as “post-COVID”, “long COVID” syndromes 125 or post-acute sequelae of COVID-19 18, and it was shown that beyond the first 30 days of illness, COVID-19 survivors exhibit a significantly higher risk of death and health resource utilisation. 126 In relation to metabolic diseases, a recent study from Spain investigating the long-term outcomes of 766 patients with COVID-19 one year after hospital discharge, shows that 1·3% of these patients developed new-onset diabetes and in 10·1% of the patients, a worsening in glycaemic control was documented. 17 An Italian study showed that glycaemic abnormalities could be detected at least two months after recovery from COVID-19. 83

COVID-19 survivors frequently develop physical, psychosocial and cognitive impairments requiring rehabilitation programmes. 127 Prolonged exposure to stressors, such as those experienced through isolation, increases the risk of developing major depression, anxiety and post-traumatic stress disorders. 128 Furthermore, following treatment in the ICU, persistent mental health impairment is commonly described and a high prevalence of depression has been observed. 129 Additionally, it has to be considered that certain therapies impacting expression of ACE2 might also influence the RAAS and the neuroendocrine stress axis. 38 Also unexpected problems may occur after COVID-19, such as invasive fungal sinusitis (mucormycosis) usually affecting people with poor immunity and those with uncontrolled diabetes. Other risk factors for mucormycosis include steroid treatment meaning that the high doses of steroids administered to severe COVID-19 patients might induce this side-effect as recently shown in India. 130

People post discharge following COVID-19 will need close monitoring for risk factor control with potential use of novel therapies to reduce risk for medium term complications. 131 Recent follow-up study of people discharged following admission with COVID-19 showed that at a mean follow-up of 140 days, nearly a third of patients were re-admitted and 12% had died. 132 Post COVID follow-up will include assessment and monitoring of cardiovascular and renal complications and risk factor control. Those with admission hyperglycaemia will need follow-up to determine if these patients have new-onset diabetes.

The disproportionate excess mortality risk of COVID-19 in people with diabetes warrants vaccination prioritisation (Table 2). This is included in most of the national vaccination strategies. 133,134 After vaccination, disease management should follow evidence-based guidelines for COVID-19 patients with type 2 diabetes. 98 The ongoing COVID-19 tsunami in India, occasioned by the second wave, the rampant spread in both Turkey and Brazil, undoubtedly is of serious concern particularly as these countries have high prevalence of diabetes mellitus. 135-137 This represents a huge number of persons living in spaces currently facing an explosion of new COVID infections. The implications of this situation may be far reaching, particularly on the care for patients with diabetes mellitus, other metabolic diseases and their outcomes including mortality. In Africa, the situation is seemingly different, even though the emergence of new variants of COVID-19 are raising concerns. Reasons for the less severe morbidity and mortality in Africa may include; young population, quick action, public support, favourable climate and good community health system. 138 Being a resource-restricted region, Africa, particularly Sub-Saharan Africa, should lay more emphasis on prevention.

Smart disease management in and after the pandemic has been proposed. Such an integrated model of digital disease management may significantly relieve the pandemic burden to ambulatory health care if it is implemented as an interoperable digital solution, following evidence-based medical knowledge, operated by addressing the personal need of the patients and hosted by an approved medical body. 139,140 Mandatory requirements are: (1) the patient must have access to evidence-based health information in a health literacy adjusted language, (2) there must be medical indicators representing the therapeutic goal or therapeutic corridor for patients, (3) this indicator must be technically measurable and (4) the patient must have a therapy that can be adjusted by patient self-management. Applying smart digital disease management may have the potential to significantly reduce the throughput in the ambulatory health care system. 141 This is an option in regions with a fast-growing prevalence of patients with chronic diseases such as Africa particularly the sub-Saharan region, or regions with a reduction of density of medical services worldwide. Finally, it may be the optional virtual solution for ambulatory care for patient with chronic diseases in pandemic times.

**Conclusions**

The pandemic has presented unique challenges for people with metabolic diseases, a group who has a high-risk for severe COVID‐19 infection. Pending definitive evidence regarding the long-term effects of COVID-19 on risk of incident diabetes, the vulnerability of islet/beta cells to inflammation and oxidative stress is well supported by clinical and experimental studies. This is against the backdrop of the tiny amount of beta cells, which are one of the most metabolically active cells in our body. 142

There has been increased emphasis on the importance of self‐care activities for people with diabetes to optimise their diabetes management; however, this has proven difficult because of restrictions due to lockdown and reduced face‐to‐face diabetes education. 143 During the pandemic, we have learned how to optimise pharmacological diabetes management for patients affected by diabetes without and with COVID-19 including ICU treatment. 12,98 The pandemic has also presented people with diabetes and their healthcare teams with an opportunity to innovate and move quickly towards increasingly digitalised care, to continue supporting people with diabetes from their own homes 144. Preventive measures including an increase in physical activity and enhanced health nutrition gain importance to break insulin resistance and should be effective to reduce COVID-19 related mortality.

The COVID-19 pandemic has demonstrated the inherent inertia and limitations of our global health care systems. It would be a progressive failure if we do not take this alarm signal and change our strategies to prevent diabetes and obesity with societal measures, diagnose the disease at its earliest stages, focus on remission of diabetes, rather than progressive and expensive treatment and individualise diabetes management to meet sustainable prevention of complications by using all evidence and technology available to us. The vulnerability of countries/areas with ill-prepared systems notably the low income countries and that of the disadvantaged community with knock-on effects on the global community calls for urgent actions to close these care gaps by reforming the health care system, which was recently highlighted in the Lancet Commission on Diabetes. 145

The corona virus and its follow-up diseases will probably accompany us for the next many years meaning that we have to learn to live with the virus and be aware of possible complications especially for people with diabetes and other metabolic diseases. Indeed the non-communicable pandemic of patients with metabolic disease due to diabetes and obesity affecting 0·5 billion patients worldwide may be considered as a fertile ground for the communicable pandemic of COVID-19 particularly affecting this group of the population (Fig. 3).

In the Western countries there is a high prevalence of metabolic diseases and also a high incidence of COVID-19. However, in non-Western countries where the prevalence of metabolic diseases is lower, the numbers of people with COVID-19 is unclear as those countries often have less testing for SARS-CoV-2. Therefore, a question still remaining to be fully answered is whether the risk to be infected is the same for everybody or if based on the specific receptor pathways there is a higher risk for patients with metabolic diseases to get infected in the first place.

**Contributors**

CS, PEHS, AL, RL and SRB wrote several sections of the review. Remaining authors wrote smaller sections of the review. CS and RL prepared the figures. CS, PEHS and RL prepared the tables. All authors reviewed successive drafts of the Review. All authors approved the final submitted version.

**Declaration of interests**

KK has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG / Menarini Group, Janssen, and Napp. ER reports personal fees as consultant/advisor for Abbott, Air Liquide, Astra-Zeneca, Boehringer-Ingelheim, Cellnovo, Dexcom, Eli Lilly, Insulet, Johnson & Johnson (Animas, LifeScan), Medirio, Medtronic, Novo Nordisk, Roche Diagnostics, Sanofi-Aventis and Tandem, and research grant/material support from Abbott, Dexcom, Insulet, Roche Diagnostics and Tandem.

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**Figure Legends**

**Figure 1. The renin-angiotensin-aldosterone-system in COVID-19**. **A.** When the RAAS is activated due to e.g. low blood pressure, angiotensinogen produced in the liver is cleaved to angiotensin I (Ang I) in the kidney. Ang I is further converted to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). Ang II binds to its receptors Ang II type 1 and 2 receptors (AT1R and AT2R) causing the release of aldosterone from the zona glomerulosa in the adrenal cortex, vasoconstriction and adverse remodelling of vascular wall and myocardium. This part of the RAAS system serves as a vasoconstrictor. In the second part of the RAAS, Ang II is converted by ACE2 to the vasodilatory Ang 1-7, which binds to its mitochondrial assembly (MAS) receptor thereby possessing opposing actions of Ang II and ACE. **B.** ACE2 consists of two forms, a membrane-spanning protein and a circulating soluble form (sACE2) both capable of binding the spike protein on the surface of SARS-CoV-2. The expression of ACE2 is regulated by HMBG1 and SMARCA4. Upon infection with SARS-CoV-2, the viral spike protein is cleaved by TMPRSS2 and the membrane form of ACE2 is internalised together with the virus leading to a decrease in the ACE2 concentration. This may result in overactivation of the ACE/Ang II part of the RAAS and thereby an augmented signalling through AT1R and AT2R. Virus entry is facilitated by NRP1 promoting the interaction between SARS-CoV-2 and ACE2. A suggested alternative receptor for virus entry is DPP4.

**Figure 2. Diabetes/obesity and COVID-19**. Several clinical manifestations and complications of diabetes/obesity and COVID-19 are similar. In the white adipose tissue of individuals with obesity, the adipocytes are hypertrophic and the tissue is infiltrated with pro-inflammatory immune cells secreting cytokines, chemokines and adipokines leading to a permanent inflammatory phenotype. Also in diabetes, insulin resistance leads to an increased infiltration with M1 macrophages in adipose tissue. Upon infection with SARS-CoV-2, this chronic inflammation may aggravate COVID-19 symptoms in a synergy effect resulting in metaflammation and cytokine storm contributing to severe COVID-19 disease.

**Figure 3. Metabolic diseases drive SARS-CoV-2 infection susceptibility.** On one hand, metabolic diseases increase the risk of severe COVID-19. On the other hand, COVID-19 may lead to new-onset metabolic diseases or worsening of already existing metabolic disorders.

|  |  |
| --- | --- |
| **Medications with potential interfering effects on COVID-19** | |
| **Potential positive effects** | **Potential negative effects** |
| **Glucocorticoids**   * **Anti-inflammatory effect 73**   **ACE inhibitors/Ang II receptor blockers 38**   * **Increased expression of soluble ACE2, neutralization of virus 34**   **Metformin 100,101**   * **Reduces blood glucose levels** * **ACE2 stability** * **Modulates ACE2/Ang II/AT1R axis** * **Inhibits host-virus binding** * **Mitochondrial Complex I inhibition** * **Endothelial/vascular protection** * **Decreases virus maturation**   **Sodium-glucose-co-transporter 2 inhibitors 57**   * **Reduce blood glucose levels** * **Reduces viral load** * **Positive effects on cardiovascular and renal functions**   **Glucagon-like peptide-1 receptor agonists 108,109**   * **Reduce blood glucose levels** * **Anti-inflammatory effects** * **Improve endothelial dysfunction** * **Improve cardiovascular and renal functions**   **Dipeptidyl peptidase-4 inhibitors 58,59**   * **Reduce blood glucose levels** * **Blockage of virus uptake** * **Reduce inflammatory response** * **Well tolerated**   **Insulin 22,113**   * **Reduces blood glucose levels** * **Anti-inflammatory effect** | **Glucocorticoids**   * **Risk of hyperglycaemia 146**   **ACE inhibitors/Ang II receptor blockers 38**   * **Increased expression of membrane-bound ACE2, might increase virus entry (no clinical evidence) 33**   **Metformin 100,101**   * **Risk of dehydration and lactic acidosis** * **Chronic kidney disease** * **Acute kidney injury**   **Sodium-glucose-co-transporter 2 inhibitors 22**   * **Risk of dehydration** * **Diabetic ketoacidosis** * **Acute kidney injury**   **Glucagon-like peptide-1 receptor agonists 22**   * **Reduce appetite and increase satiety** * **Gastrointestinal symptoms**   **Dipeptidyl peptidase-4 inhibitors 57**   * **Increase mortality in elderly patients 57**   **Insulin 77, 117**   * **Hypoglycaemia** * **High doses increase COVID-19 mortality** |

**Table 1.** Glucose-lowering medications with potential interfering effects on COVID-19 according to current knowledge and guidelines as referred. Of note, many of these results are retrospective and confounded by indications, patients’ risk profiles, and/or severity of diseases.

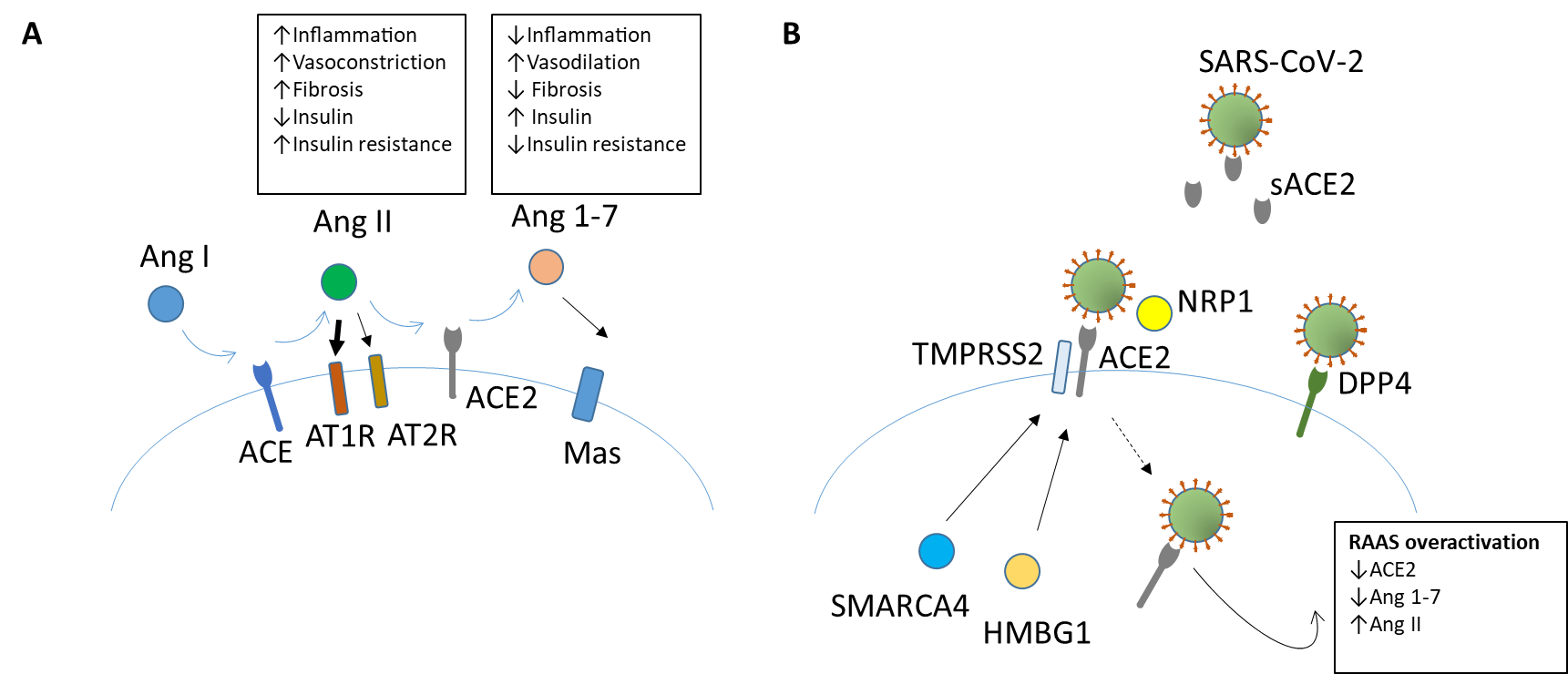
|  |
| --- |
| Management of metabolic diseases in a pandemic situation |
| * Prevention of infection: Avoid social contact 147 * Vaccination: Prioritisation 133,134 * Improve a healthy lifestyle also during lockdown and quarantine 22 * Individual management: Establish an individual set of self-management goals (measurement rate, body weight, steps per day, waist circumference, blood pressure) and adhere to these goals consistently 148 * Digital support: Make use of online education, virtual consultation and digital health (temperature, physical activity, body weight, waist circumference, blood pressure) 149 * Behavioural support: Use digital stress management tools to increase resilience and stress resistance 144 * Intensify foot care 150 * Check for new diabetes 83 * Cardiac risk management 9 * Adhere to lipid-lowering drugs 57,68 * In chronic kidney disease monitor urinary excretion and oedema 12 * Optimise metabolic and blood pressure control 149 * Perform intensified glucose monitoring (SMBG, 5xd; FGM/CGM) to identify early deterioration of glycaemic condition as well as monitoring blood pressure if hypertensive 149 * Glucose in target range 22:   + Plasma glucose concentration 4–8 mmol/L (72–144 mg/dL)   + On the ICU plasma glucose should be 6·7-11·1 mmol/L (120-200 mg/dL)   + Avoid hypoglycaemia Grade 2 (<54 mg/dL; <3·0 mmol/L) and Grade 3   + HbA1c less than 53 mmol/mol (7%) |

**Table 2.** Recommendations of metabolic disease management in a pandemic situation based on recent literature.

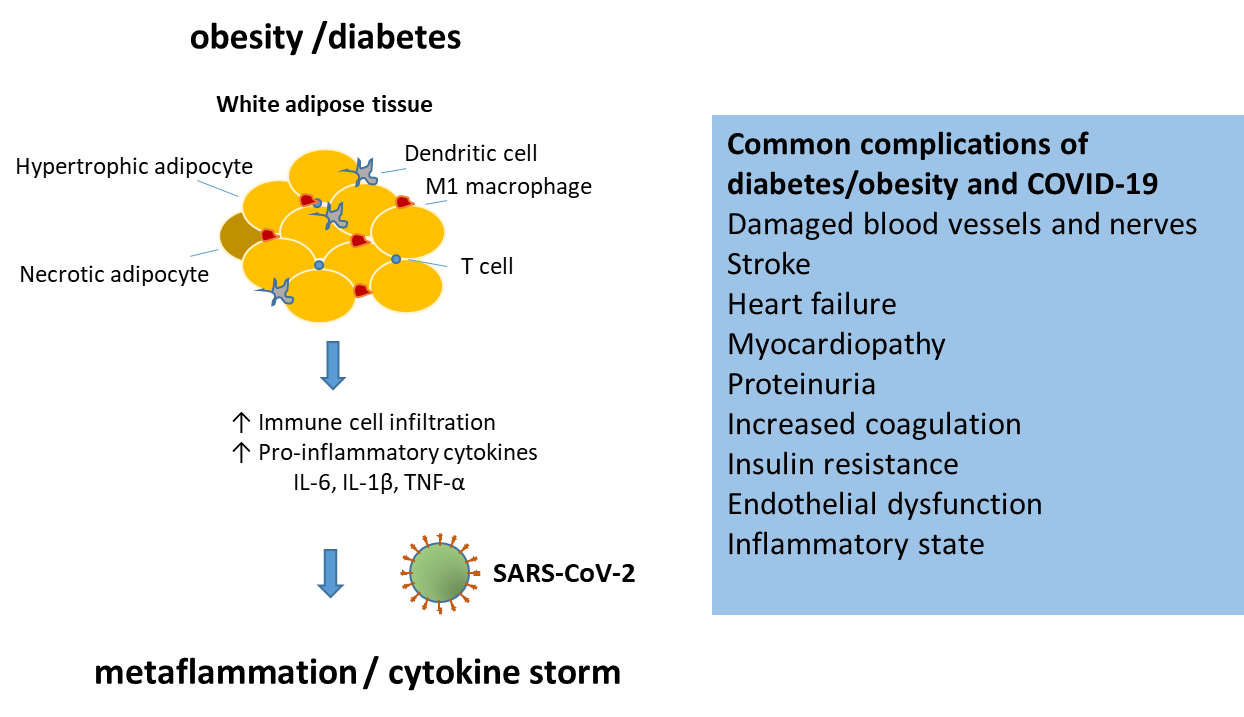
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| --- | --- | --- | --- | --- |
|  | **No COVID-19** | **Mild disease**  **(Primary care)** | **Moderate disease (Hospital)** | **Severe disease**  **(ICU)** |
| Recommended according to guidelines | Metformin  DDP4 inhibitors  SGLT2 inhibitors  GLP-1 RA  Sulfonylurea  α-Glucosidase inhibitors  TZD  Insulins | Metformin  DPP4 inhibitors  SGLT2 inhibitors  GLP-1 RA  Insulins  Sulfonylurea  α-Glucosidase inhibitors | DPP4 inhibitors  SGLT2 inhibitors  GLP-1 RA  Insulins | DPP4 inhibitors  Insulins |
| Use with caution |  | TZD | Metformin  α-Glucosidase inhibitors  SGLT2 inhibitors |  |
| Contraindications |  |  | TZD  Sulfonylurea | Metformin  α-Glucosidase inhibitors  SGLT2 inhibitors  TZD |

**Table 3.** Recommended antidiabetic management of COVID-19 patients. 68,98

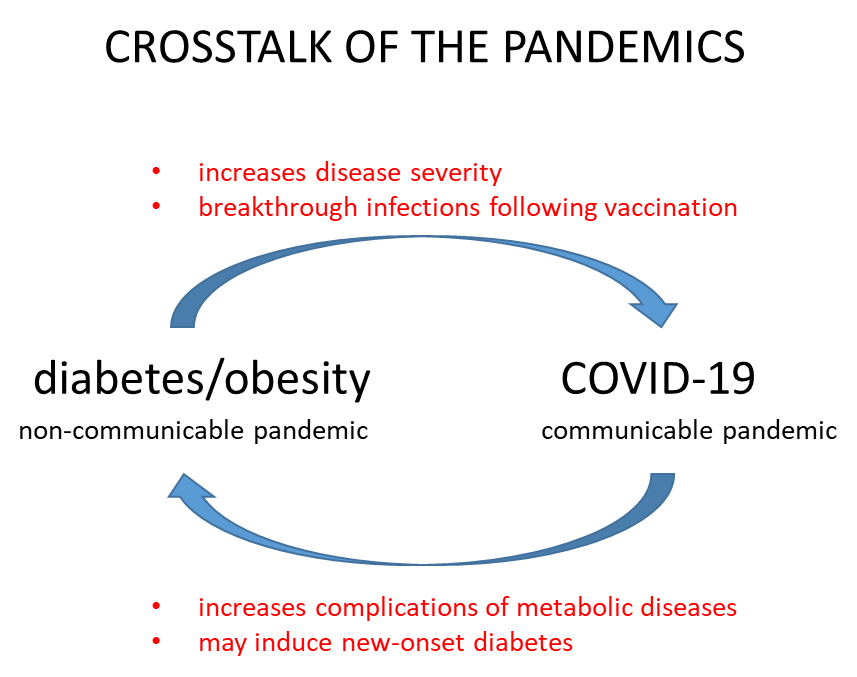
**Figure 1**

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**Figure 2**

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**Figure 3**

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