Diabetes and COVID-19: The past, the present, and the future

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ABSTRACT

Diabetes, one of the most prevalent chronic diseases in the world, is strongly associated with a poor prognosis in COVID-19. Scrupulous blood sugar management is crucial, since the worse outcomes are closely associated with higher blood sugar levels in COVID-19 infection. Although recent observational studies showed that insulin was associated with mortality, it should not deter insulin use in hospitalized patients requiring tight glucose control. Back and forth dilemma in the past with regards to continue/discontinue certain medications used in diabetes have been mostly resolved. The initial fears of consequences related to continuing certain medications have been largely dispelled. COVID-19 also necessitates the transformation in diabetes care through the integration of technologies. Recent advances in health-related technologies, notably telemedicine and remote continuous glucose monitoring, have become essential in the management of diabetes during the pandemic. Today, these technologies have changed the landscape of medicine and become more important than ever. Being a high-risk population, patients with type 1 or type 2 diabetes, should be prioritized for vaccination. In the future, as the pandemic fades, the prevalence of non-communicable diseases is expected to rise due to lifestyle changes and medical issues/dilemma encountered during the pandemic.

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1. Introduction

More than a year has passed since the emergence of coronavirus disease of 2019 (COVID-19) caused by the respiratory virus, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) from Wuhan, China. Numerous risk factors for severe COVID-19 and poor outcome have been identified from observational studies and clinical trials. One of the well-known risk factors is diabetes mellitus (DM), one of the most prevalent chronic diseases worldwide, with a estimated prevalence of 9.3%, and frequently co-exists with other comorbidities in the form of metabolic syndrome [1]. Early data from the epicenter showed that DM is one of the most common comorbidities, only second to hypertension [2,3].

DM was strongly associated with morbidity and mortality in patients with COVID-19 [4].

Considering the prevalence of DM and its strong impact on COVID-19 related outcomes, it is imperative to explore and obtain the best available evidence to improve patients' outcome in patients with diabetes.

In this narrative review, we aimed to highlight diabetes as a factor that increases susceptibility to COVID-19, poor COVID-19 related outcomes, the three most pertinent aspects of managing diabetes in times of COVID-19, and what the future holds for diabetes post-pandemic. Finally, we emphasized the importance of vaccinating patients with diabetes and the rationale underlying it.

2. Diabetes and susceptibility to COVID-19 infection

Data that emerged from Wuhan, China, early in the pandemic indicates that diabetes was prevalent in patients hospitalized with COVID-19. Similarly, diabetes is one of the most common comorbidities, other than hypertension and obesity in Lombardy, Italy, and New York, USA [5,6]. Previously, studies have shown that patients with diabetes were more susceptible to Middle East Respiratory Syndrome (MERS) and Severe acute respiratory syndrome (SARS) infection, due to dysregulated immune response leading to severe and extensive lung pathology [7]. Thus, it is unsurprising if this population is also at an increased risk of acquiring COVID-19 infection.

Several molecular pathomechanisms may render patients with diabetes vulnerable to COVID-19, explained as follows. Firstly, diabetes was associated with a decreased phagocytic activity, neutrophil chemotaxis, diminished T cell function, and lower innate and adaptive immunity in general [8–10]. Furthermore, patients with diabetes had

higher angiotensin-converting enzyme-2 (ACE2) levels than the general population [11]. ACE2 serves as an entry receptor for the SARS-CoV-2 due to its high binding affinity, which is expressed ubiquitously in human lung alveolar cells, cardiomyocyte, vascular endothelium, and other various sites [12–15]. Consequently, the SARS-CoV-2 has a high affinity for cellular binding and viral entry with decreased viral clearance [10]. Thirdly, elevated glucose level directly increases SARS-CoV-2 replication with possible lethal complication due to dysregulation of the immune system and inflammatory response [15]. This phenomenon is well demonstrated in human monocytes where elevated glucose level and glycolysis mediate mitochondrial reactive oxygen species production and activate hypoxia-inducible factor 1α, which increases viral replication [15,16]. Lastly, there might be direct implications between glucose impairment and cytotoxic lymphocytes natural killer (NK) cell activity. A multiple regression analysis shows that the HbA1c level serves as an independent risk factor for NK cell activity [17]. Compared to patients without T2DM, lower NK cell activity is found in patients with pre-existing Type 2 diabetes (T2DM) and prediabetes [17]. Nevertheless, to the best of the authors' knowledge, there is no solid real-world data that shows increased susceptibility to SARS-CoV-2 infection in patients with diabetes, despite the theoretical risk [18].

3. Diabetes and poor outcomes of COVID-19 disease

Since the early pandemic, diabetes has been identified as a risk factor for poor outcomes in the COVID-19 disease, such as progression to acute respiratory distress syndrome (ARDS) and mortality. Nonetheless, early data accrued from several observational studies, despite being timely, have poor quality in general because the emphasis on the rapidity, which sacrificed important epidemiologic fundamentals. Thus, it precludes a complete understanding of diabetes and other comorbidities and their impact on COVID-19 [19]. Here we described meta-analyses and several important observational studies that greatly contribute to our understanding on DM and COVID-19.

In a meta-analysis of 6452 hospitalized COVID-19 patients involving 30 studies, those with DM were at twice the increased risk for mortality and disease severity. A major limitation of this meta-analysis was patient duplication and repeated analysis, which may show misleading results [4].

Another meta-analysis of the same topic but addressing this problem showed that the prevalence of DM in hospitalized COVID-19 patients was 12%. Moreover, DM was associated with a higher risk for intensive care unit (ICU) admission (relative risks (RR) of 1.96 [95%CI 1.19, 3.22; n = 8890; I^2: 80%; p = 0.008]) and mortality (RR of 2.78 [95% CI 1.39, 5.58; n = 2058; I^2: 75%; p < 0.001]), but not severe disease [20]. Nevertheless, this study cannot exclude the effect of confounders.

A whole-population study in England encompassing 61,414,470 individuals found that diabetes is found in one-third of non-survivors. In a multivariate analysis, compared to their non-diabetic counterparts, the odds ratios (ORs) for in-hospital mortality were 2.86 (95% CI 2.58, 3.18) type 1 diabetes mellitus (T1DM) and 1.80 (95% CI 1.75, 1.86) for T2DM. However, these findings are limited because residual confounders (smoking history, body mass index (BMI), incomplete cardiovascular comorbidities) not addressed by the model [21].

Several risk factors associated with mortality in England due to COVID-19 in T1DM and T2DM patients have been identified through a population-based cohort study by Holman et al. [22]. Utilizing a national dataset of patients with diabetes registered in general practice, they found that, other than the well-known risk factors, this study identified glycemic control (HbA1C), and BMI as independent predictors of the primary outcome, i.e. COVID-19 related death. Compared to patients with HbA1C of 48–53 mmol/mol (6.5–7.0%), those with HbA1C of ≥86 mmol/mol (10.0%), were at 113% and 61% increased risk of COVID-19 related death in patients with T1DM and T2DM, respectively. Additionally, they found that patients younger than 70 years old were at excess risk. Significantly, this study added the body of evidence of social determinants of health (SDoH), as evidenced by increased HRs for the most deprived population and minorities (Black, Asian, and minority ethnicities).

In another prospective cohort study, involving all Scottish populations, T1DM and T2DM people were at increased cumulative risks of fatal or critical-care treated COVID-19 vs. those without, even after age and sex adjustment, with their respective ORs of 2.40 (95% CI 1.82, 3.16; p < 0·001) and 1.37 (95% CI 1.28, 1.47; p < 0.001) [23].

More importantly, this study showed that among people with diabetes, collectively those with more severe DM and in vulnerable populations (living in a residential care or deprived area), and smokers were more likely to develop outcomes, which remained significant after adjusting for age, sex, and diabetes type and duration.

Meanwhile, a nationwide retrospective cohort study from the UK evaluating COVID-19 Hospitalisation in England Surveillance System (CHESS) found that COVID-19 patients with T2DM hospitalized in the critical setting (high dependency unit (HDU) and ICU were at 23% increased risk all-cause mortality; adjusted hazard ratio (aHR) of 1.23 [95% CI 1.14, 1.32]), which was lower than the aforementioned studies [24]. Importantly, the aHR for the younger age group (age 18–49 years) were significantly higher compared to the older groups (50–64 and ≥65 years old), with aHR of 1.50 [95% CI 1.05, 2.15] vs. 1.29 [1.10, 1.51] and 1.18 [1.09, 1.29], respectively.

A major study addressing DM in COVID-19 originates from France. The COVID-19 SARS-CoV-2 and Diabetes Outcomes (CORONADO) is a retrospective cohort study involving 68 French Hospitals with the main aim to characterize phenotypically hospitalized patients with DM and COVID-19 [25]. Several important observations arose from this study. First, BMI was the single pre-admission variable that was associated with the primary outcome, i.e., composite of tracheal intubation and/or death within 7 days of admission. Second, several laboratory examinations at admission were associated with the primary outcome, namely lymphocyte count, c-reactive protein level (CRP), and aspartate aminotransferase (AST). Micro and macrovascular complications related to diabetes were associated with the risk of death on day 7. Surprisingly, long-term glucose control (HbA1C levels) was not associated with the primary outcome. Nevertheless, substantial HbA1C levels that were missing remain a caveat before drawing a definite conclusion. The same investigators also established prognostic factors associated with discharge and death within 28 days, these include microvascular complications, dyspnoea on admission, routine anticoagulant therapy, higher AST, CRP levels, and white cell count. Interestingly, statin and insulin therapy were associated with higher deaths within 28 days [26]. Additionally, these investigators also highlighted hospitalized COVID-19 patients with T1DM, with the prevalence of 2.1%, much lower than the general population, i.e., 5.6%. Furthermore, compared to their T2DM counterparts, these patients were at half of the risk of death on D7 (10.6% vs. 5.4%). Notably, the T1DM group was significantly younger than the T2DM group ((56.0 ± 16.4 vs. 70.5 ± 12.5 years), with those <55 years were three times less likely to achieve primary outcome of death/intubation on day 7 than the T2DM group [27].

In a prospective study, Gregory et al. found that T1DM triples the risk of COVID-19 related hospitalization and severity of illness that persists after adjustment for confounders. Their respective OR were 3.90 (95% CI 1.75, 8.69) and 3.35 (95% CI 1.53, 7.33). Importantly, this study highlighted the probability of patients with T1DM to be hospitalized were at 15–22%, which was substantially higher than those without (5%). Additionally, this study highlighted the impact of SDoH on the severity of outcome, primarily in the underserved populations. Consistently, the role of SDoH was also seen in another multisite cross-sectional study involving 113 cases of T1D patients with COVID-19 [28]. Moreover, long-term glucose control (HbA1C levels) was the only significant predictor for hospitalization, with higher HbA1C associated with 43% increased risk (OR 1.43 [95% CI 1.16, 1.82]). The finding of selected studies on diabetes and poor outcome in COVID-19 is summarized in Table 1.

Table 1
Summary of studies on diabetes and poor outcomes.

Author	Summary of findings
Chen Y	Older age (per one year adjusted OR [aOR] 1.09 [95% CI 1.04, 1.15] per year increase; p = 0.001) and elevated C-reactive protein (aOR 1.12 [95% CI 1.00, 1.24]; p = 0.043) were associated with in-hospital death. Insulin utilization was associated with poorer prognosis (aOR 3.58 [95% CI 1.37, 9.35]; p = 0.009)
Cariou, B	- BMI remained positively associated with the primary outcome (tracheal intubation and/or death within 7 day of admission) (OR 1.28 [95% CI 1.10, 1.47]). On admission, dyspnoea (OR 2.10 [95% CI 1.31, 3.35]), lymphocyte count (OR 0.67 [0.50, 0.88]), C-reactive protein (OR 1.93 [95% CI 1.43, 2.59]) and AST (OR 2.23 [95% CI 1.70, 2.93]) levels were independent predictors of the primary outcomes. - Age (OR 2.48 [95% CI 1.74, 3.53]), treated obstructive sleep apnoea (OR 2.80 [95% CI 1.46, 5.38]), and microvascular (OR 2.14 [95% CI 1.16, 3.94]) and macrovascular complications (OR 2.54 [95% CI 1.44, 4.50]) were independently associated with the risk of death on day 7. - Neither long term glycemic control nor routine therapies (DPP4, RAAS blockers) were associated with COVID-19 severity.
Barron, E	The ORs for in-hospital mortality with COVID-19 were 2.86 [95% CI 2.58, 3.18] for people with T1DM and 1.80 [95% CI 1.75, 1.86] for people with T2DM compared with people without known diabetes
Gregory JM	- T1DM patients had adjusted OR of 3.90 [95% CI 1.75, 8.69] for hospitalization and 3.35 [95% CI 1.53, 7.33] for greater illness severity, which was similar to risk in T2DM. - COVID-19 outcome severity in T1DM is associated with glycemic, vascular, and socioeconomic risk factors.
McGurnaghan, SJ	T1 and T2DM were associated with substantially increased risk of fatal or critical care unit-treated COVID-19. Overall OR for diabetes, adjusted for age and sex, was 1.395 [95% CI 1.30, 1.494]; p < 0·0001, compared with the risk in those without diabetes. The OR was 2.396 (95% CI 1.82, 3.16; p < 0.0001) in T1DM diabetes and 1.369 (95% CI 1.28, 1.47; p < 0.0001) in T2DM.
Holman, N	- HbA1c is associated with COVID-19-related mortality in people with both types of diabetes. In people with T2DM, risk was significantly higher in those with an HbA1c of 59 mmol/mol (7.6%) or higher than in those with an HbA1c of 48–53 mmol/mol (6.5, 7.0%), and the risk increased with increasing HbA1c levels. - Increased COVID-19-related mortality was associated not only with cardiovascular and renal complications of diabetes but, independently, also with glycemic control and BMI. The independent association of BMI with risk of COVID-19-related death in these diabetes populations was U-shaped, with a nadir at a BMI of 25.0–29.9 kg/m^2.
Huang, I	A meta-analysis showed that diabetes in COVID-19 was associated with mortality (RR 2.12 [95% CI 1.44, 3.11], p < 0.001), severe COVID-19 (RR 2.45 [95% CI 1.79, 3.35], p < 0.001), ARDS (RR 4.64 [95% CI 1.86, 11.58], p = 0.001), and disease progression (RR 3.31 [95% CI 1.08, 10.14], p = 0.04)
Bello-Chavolla, OY	- Predictive score for COVID-19 lethality included age ≥ 65 years, diabetes, early-onset diabetes, obesity, age < 40 years, CKD, hypertension, and immunosuppression significantly discriminates lethal from non-lethal COVID-19 cases (C-statistic = 0.823).
Dennis JM	In COVID-19 patients with severe symptoms admitted to the HCU or ICU, T2DM was an independent prognosticator of survival, and greatest in the younger people. Full covariates set adjustment model All patients: 1.23 [95% CI 1.14, 1.32], p = 0.001 HCU patients: 1.19 [95% CI 1.08, 1.31], p = 0.001 ICU patients: 1.24 [95% CI 1.11, 1.38], p = 0.001
Targher, G	The proportion of severe COVID-19 illness increased progressively (p < 0.0001 by the Fisher's exact test) in relation to glucose abnormalities at admission: 7.1% in patients with random plasma glucose < 5.6 mmol/L (n = 127; mean ± SD: 4.95 ± 0.4 mmol/L), 20.3% in those with random plasma glucose 5.6–11 mmol/L (n = 153; mean ± SD: 7.03 ± 1.3 mmol/L), 25.6% in those with previously known diabetes (n = 39; mean ± SD: 9.32 ± 5.1 mmol/L), and 65.0% in those with random plasma glucose = 11.1 mmol/L at hospital admission (n = 20; mean ± SD: 12.0 ± 3.7 mmol/L), respectively. In hospitalized middle-aged Chinese patients with laboratory-confirmed COVID-19, the presence of diabetes at hospital admission was strongly associated with an increased likelihood of having severe COVID-19 illness.
Seiglie, J	Age and higher CRP levels were potential predictors and risk stratification for patients who are prone to in-hospital death. Poorer outcome in insulin group mandates further elucidation through prospective cohort study or clinical trials
Wargny, M	Hospitalized patients with T1DM have lower risk of severe prognosis, especially younger ones compared to their T2DM counterparts (56.0 ± 16.4 vs. 70.5 ± 12.5 years, p < 0.0001)

HCU: High Care Unit.
ICU: Intensive Care Unit.
CRP: C-reactive protein.
DPP4: Dipeptidyl Peptidase – 4.
OR: Odds Ratio.
RAAS: Renin angiotensin aldosterone system.
RR: Risk Ratio.
T1DM: Type 1 Diabetes Mellitus.
T2DM: Type 2 Diabetes Mellitus.

4. Obesity and DM

Patients with underlying chronic illnesses, which often co-exists in patients with diabetes, have an increased risk of developing severe COVID-19 with higher mortality and ICU admission [5,15,22,29–31]. Reasons for poorer outcomes in COVID-19 patients with DM have been described in detail elsewhere [32]. Notably, we highlighted T2DM and obesity due to similar pathomechanisms between them [33]. Obesity frequently co-exists with diabetes and is unequivocally associated with poorer outcomes in COVID-19 infection. Several reasons may explain poor outcomes associated with obesity, as follows. First, obesity may worsen respiratory distress in COVID-19 by hampering the respiratory mechanics, reducing minute ventilation, and reducing functional reserve capacity [34]. Furthermore, obesity is associated with chronic low-grade inflammation. Visceral fat produces inflammatory cytokines (inflammokines) and ACE2 receptors on visceral fat are

a possible site of viral replication, which consequently causes a higher viral burden in obese patients [35,36]. Therefore, in the background of heightened inflammatory state, COVID-19 infection may trigger a cytokine storm. Also, obesity is associated with higher events of thromboembolic events. Compounded with COVID-19 infection, which is associated with a prothrombotic event, the thromboembolic risk may increase several-fold [37,38].

Historically, obese patients were at lower risk of death due to pneumonia and ARDS. This phenomenon is known as the obesity paradox [34,39]. Nevertheless, accumulating body of evidence refute this mortality benefit seen in obese patients. The NHS study from England found that the relationship between BMI and COVID-19 related death was a U-shaped curve. Both for T1D and T2DM, the HRs were at a nadir when BMI was 25.0–29.9 kg/m^2. Contrastingly, BMI < 20.0 kg/m^2 and ≥40.0 kg/m^2 were at HRs of 2.45 [95% CI 1.60, 3.75], p < 0.0001 and 2.33 [95% CI 1.53, 3.56, p < 0.0001] for T1D, and at HRs of 2.33 ([95% CI 2.11, 2.56], p < 0·0001)

and 1.60 (95% CI 1.47, 1.75, p < 0.0001) for T2DM, respectively [22]. Consistent with these observations, a part of CORONADO study also found that compared to normal BMI (18.5–24.9 kg/m^2) with T2DM, overweight (OR 1.65 [95% CI 1.05–2.59]), class I obesity (OR 1.93 [95% CI 1.19–3.14]), and class II/III obesity (OR 1.98 [95% CI 1.11–3.52]) were associated with increased risk of achieving a primary outcome in hospitalized COVID-19 patients [40]. Interestingly, this observation only exists in patients <75 years old. Several studies indicate that visceral adiposity, but not subcutaneous adiposity, was significantly associated with poor outcome in patients with COVID-19 [41–43], the apparent benefit or null-effect of obesity in some circumstances might be explained by variation related to visceral adiposity.

Bello-Chavola et al. showed that almost half of the impact of diabetes on lethality (49.5%), was attributable to obesity [44]. Notably, diabetes that occurred in the Mexican is a distinct phenotype, i.e., early-onset diabetes, which is associated with obesity, a rapidly declining β cell function, and a higher risk of microvascular complications.

5. Management of diabetes in times of COVID-19 pandemic

A detailed description of diabetes management in COVID-19 patients and in general amid the pandemic is available on previous review articles [45–48]. We underscored the three most pertinent aspects of diabetes management: i.e. health-related technologies, blood glucose controls, and antidiabetic agents and their mechanisms relating to immunomodulators.

5.1. Health-related technologies

Before the pandemic, there was sparse adoption of health-related technologies in managing diabetes, with the pediatrics field leading the race. Now, the COVID-19 pandemic has transformed our healthcare systems dramatically and necessitated the early adoption of these technologies [49].

Overall, two health-related technologies played crucial parts amid the pandemic, i.e., telemedicine and remote continuous glucose monitoring (rCGM).

Ushigome et al. have investigated the usefulness and safety of remote CGM (Dexcom G4 Platinum CGM System) in a patient with T2DM and covid-19 in a 68-years-old man [50]. Despite increased insulin needs for the patient (0.8 to 6.8 unit/h), hypoglycemic events were prevented, with the glucose range of 100–350 mg/dL. Also, rCGM led to decreased invasive procedures for blood glucose (BG) testing, consequently decreasing contact with healthcare workers (HCWs).

In a case-series, the combination of telehealth monitoring and CGM enabled patients with diabetic ketoacidosis to be managed as outpatients. Telemedicine has increased accessibility to providers for T1D patients. Meanwhile, telemedicine and patient's BG data provided by the CGM enabled providers to manage T1D optimally. This is reflected in the series, wherein one patient with a new-onset T1D, her BG levels were only 13% in time in range (TIR; 70–180 mg/dL) on day one, and improved significantly on day 12 with TIR more than 90% and none in time below range (TBR; <70 mg/dL) [51].

Another series by the same group highlighted the successful management of new-onset T1D through telemedicine with the help of CGM [52]. Two patients (20-year-old white male (patient 1) and 12 months white female (patient 2) with new-onset T1DM were initially treated in Barbara Davis Center for Diabetes and subsequently discharged for telehealth monitoring. Patient 1 experienced improvement in TIR glucose levels from 16 to 37 to 91% with no TBR, while improvement between meals and overnight glycemic profiles over the course of 2 weeks was seen in patient 2.

Moreover, another series showed that rCGM initiation through telehealth in 34 DM patients (27 T1D, 7 T2DM on insulin) was sustainable, with usage rate nearing 95% and CGM was used at least 6 days/week [53]. More importantly, glycemic control improved substantially, with Mean HbA1c at 12 weeks of 7.2 ± 1.3 (baseline: 8.3 ± 1.6) and mean TIR of 59% ± 20% (baseline: 48% ± 18%), which translated to increase of TIR approximately 2.7 h/day.

Finally, two series underscored the usefulness of rCGM in the ICU settings. The first study by Agarwal et al. involving 11 critically ill patients due to COVID-19 showed that validated real-time continuous glucose monitoring (rtCGM) is a potential addition to the standard point of care (POC) glucose testing as it is feasible, acceptable, and reliable [54].

Moreover, through this technology, a 60% reduction of potential POC tests from 60 to 28, with the majority (77.7% values, n = 493) of rtCGM-POC paired values fell within 20% of those in POCs, as recommended by the FDA.

Consistently, the benefit of rCGM was evidenced in the following study. A case series involving 5 ICU patients and one ambulatory patient to identify the usefulness of a new platform designed for simultaneous monitoring demonstrated improvement in TIR in all patients and prevented hypoglycemia [55]. Notably, no adverse events reported in the monitored ambulatory patients (199 days of remote monitoring).

In summary, these two technologies are beneficial for remote management of DM and will be practice-changing in the future. Of note, however, regulatory and policy reforms for telemedicine and the provision of CGM for the underserved populations are needed if widespread adoption is meant to be reached. The finding of selected studies on diabetes technology is summarized in Table 2.

5.2. Blood glucose controls

An accumulating body of evidence showed that glycemic control is crucial for hospitalized COVID-19 patients, irrespective of diabetes status.

Analyzing the data collated by Glytec, an insulin software titration company, Bode et al. showed that among 1112 hospitalized COVID-19 with DM (+)/uncontrolled hyperglycemia (+) patients (n = 451 patients) compared to patients DM (−) and uncontrolled hyperglycemia (−) have a higher mortality rate (28.8% vs. 6.2%, p ≤ 0.001) and stay at hospital one day longer (5.6 vs. 4.3 days, p ≤ 0.001). Strikingly, hyperglycemic (+) patients had a significantly higher mortality rate compared to diabetic patients. (41.7% vs 14.8%, p ≤ 0.001) [56]. Despite several caveats, this study underscores the importance of in-hospital glycemic management.

Table 2
Summary of studies on diabetes technology.

Author	Summary of findings
Ushigome, E	Remote Continuous Glucose Monitoring was a safe and effective tool and can reduce the exposure to HCWs among Severe COVID-19 Patient with Diabetes. It reduced hospitalization days in the isolation ward and invasive procedures, increased insulin needs from 0.8 to 6.8 u/h, and maintain BG levels with range of: 100–350 mg/dL w/o hypoglycemia
Garelli, F	The utility of a new platform for simultaneous remote monitoring of multiple ICU and/or quarantined patients of Coronavirus Disease 2019 in Intensive Care Units showed that hypoglycemia did not occur in all patients.
Peters LA	The role of technology and telehealth in the form of continuous glucose monitoring and access to HCP through telemedicine, are vital for managing T1DM patients in an outpatient setting
K Satish	Telehealth is potentially practice changing with several limitations (certain population w/o knowledge of the technology, payment system precludes its widespread use). Physical examinations that can't be done are other limitations.
Agarwal	Validated real time continuous glucose monitoring (rtCGM) for critically ill patients is a potential addition to the standard point of care (POC) glucose testing as it is feasible, acceptable, and reliable.
Gal RB	Remote CGM initiation was successful in achieving sustained use and improving glycemic control after 12 weeks as well as improving quality-of-life indicators. Telehealth approach could substantially increase the adoption of CGM and potentially improve glycemic control for people with diabetes using insulin.

Similarly, the prognostic utility of blood glucose was also seen in other studies. Wu et al. demonstrated that elevated BG levels at the admission of non-critical cases were an independent risk factor for progression to critical cases/death (Hazard Ratio [HR] 1.30 [95% CI 1.03, 1.63], p = 0.026). Moreover, elevated BG levels at the time of critical diagnosis (HR 1.84 [95% CI 1.14, 2.98], p = 0.013). Progression to critical cases/death in non-critical cases and in-hospital mortality in critical cases were also seen among patients with higher BG levels during the hospital stay or after critical diagnosis. Consistently, this was also the case for patients without DM but with elevated BG levels [57].

Contrarily, when evaluating the degrees of hyperglycemia impact on all-cause mortality, hyperglycemia (fasting glucose 5.6–6.9 mmol/L and/or HbA1c 5.7–6.4%) did not increase the all-cause mortality after multiple adjustments, despite higher ICU admission and invasive mechanical ventilation (6.2% vs. 1.5; 4.7% vs. 2.3%) compared to the normoglycemic group. Furthermore, the highest risk of all-cause mortality was seen in newly diagnosed diabetes (fasting glucose ≥7 mmol/L and/or HbA1c ≥6.5%) with a HR of 9.42 [95% CI 2.18, 40.7] [58].

Zhu et al. stressed the importance of good glycemic control in patients with pre-existing DM. In their retrospective longitudinal multi-centered study involving 7339 confirmed COVID-19 cases examining the impact of diabetes status and glycemic control in patients with pre-existing type 2 diabetes mellitus on mortality rate, the authors found that T2DM significantly increased the risk of COVID-19 related death [59]. Moreover, for those with pre-existing T2DM with poor glycemic control (BG >10 mmol) compared to well-controlled BG (3.9–10 mmol), the previous group experienced higher all-cause mortality and COVID-19 related complications. The findings were still significant, even after propensity score matching, to minimize the effect of the confounder.

Fasting blood glucose (FBG) on admission also appears to be useful as a prognostic tool. The poor 30-day outcome was identified in hospitalized COVID-19 patients with elevated FBG, with a 21% increased risk of achieving outcomes after adjusting to pre-existing DM (OR 1.217 [95% CI: 1.054–1.405], p = 0.008). The optimum cutoff was ≥6.23 mmol/L, with an area under the curve of 0.817 (95% CI 0.765, 0.868), and sensitivity and specificity of 75.6% and 77.0%, respectively [60].

Intriguingly, the association between FBG and COVID-19 patients without DM is J-shaped, based on FBG's quintiles. The lowest risk was FBG at 4.74–5.78 mmol/L (second quintile), with FBG quintiles below or above this range associated with severe COVID-19/critical condition. Correspondingly, the adjusted odds ratios (aOR) for the remainder quintiles were 25.33 (2.77, 231.64), 3.13 (0.33, 29.67), 10.59 (1.23, 91.24), and 38.93 (4.36, 347.48) [61].

Furthermore, hyperglycemia on admission (>7.77 mmol/L) exhibited higher interleukin-6 (IL-6) and D-Dimer levels, and clinically translated with more patients in this group achieved a composite of poor outcomes. Notably, insulin usage improved glycemic control, which consequently improved patients' outcomes [62].

Another study relating to at-admission hyperglycemia (≥7.78 mmol/L) showed that hyperglycemia, but not DM, was a consistent predictor for mortality even after adjustment for age and male gender, clinical confounders, as well as biomarkers. Furthermore, based on quintile grouping, patients with BG at Q4 and Q3 had a higher mortality rate than Q1. A threshold effect was seen in Q5, where no worsening of prognosis occurred [63].

Another important feature of FBG on COVID-19 severity is its nonlinearity, i.e., the magnitude of FBG increment and its impact on COVID-19 severity differs in different baselines. Barrack et al. showed that an increment from 5 to 10 mmol/L is associated with a substantial increase in the OR of ICU admission (36.02 [95% CI 23.63, 54.91]). Contrarily, an increment from 10 to 15 or from 15 to 20 mmol/L is associated with a much smaller increase in the OR of ICU admission. Thus, strict glucose control is paramount in preventing worse outcomes for COVID-19 patients.

Table 3
Summary of glucose levels on COVID-19 outcome.

Author	Summary of findings
Copelli A	At admission hyperglycemia was independently associated with a poor prognosis. Nevertheless, blood glucose control on hospitalized patients' outcome, remains to be elucidated
Lazarus G	High admission FBG level independently predicted poor COVID-19 prognosis. There was non-linear relationship between admission FBG and severity ($P_{\text{non-linearity}} < 0.001$), where each 1 mmol/L increase augmented the risk of severity by 33% (RR 1.33 [95% CI 1.26, 1.40]).
Zhu	T2DM is an important risk factor for COVID-19 progression and adverse endpoints, and well-controlled BG, maintaining glycemic variability within 3.9 to 10.0 mmol/L, is associated with a significant reduction in the composite adverse outcomes and death
Barrak A	a small incremental increase within the normal range of FBG was associated with a substantial increase in risk of ICU admission for COVID-19 patients (a 1 mmol/L increase in FBG was associated with 1.59 times [95% CI 1.38, 1.89], p = 0.001)
Zhu B	Of J-shaped associations between FBG and risk of severe and critical condition in non-diabetes patients with COVID-19, with nadir at 4.74–5.78 mmol/L.
Sardu, C	Insulin infusion may be an effective method for achieving glycemic targets and improving outcomes in patients with COVID-19.
Hamer, M	Higher levels of A1C within the normal range were a risk factor for COVID-19 (RR = 2.68 [95% CI 1.66, 4.33])
Klonoff, DC	Hyperglycemia and hypoglycemia were associated with poor outcomes in patients with COVID-19. Admission glucose was a strong predictor of death among patients directly admitted to the ICU. Severe hyperglycemia after admission was a strong predictor of death among non-ICU patients.
Bode, B	Among hospitalized patients with COVID-19, diabetes and/or uncontrolled hyperglycemia occurred frequently. COVID-19 patients with diabetes and/or uncontrolled hyperglycemia had a longer LOS and markedly higher mortality than patients without diabetes or uncontrolled hyperglycemia. Patients with uncontrolled hyperglycemia had a particularly high mortality rate
Zhang, B	Admission FBG was associated with poor 30-day outcome (OR 1.155 [95% CI 1.01, 1.32, p = 0.032]). After adjusting for pre-existing diabetes, the OR of FBG increased to 1.217 [95% CI 1.05, 1.41]; p = 0.008.
Wu, J	Elevation of admission blood glucose level was an independent risk factor for progression to critical cases/death among non-critical cases (HR = 1.30, 95% CI 1.03 to 1.63, p = 0.026). Elevation of initial blood glucose level of critical diagnosis was an independent risk factor for in-hospital mortality in critical cases (HR 1.84 [95% CI 1.14, 2.98, p = 0.013]. Higher median glucose level during hospital stay or after critical diagnosis (≥6.1 mmol/L) was independently associated with increased risks of progression to critical cases/death among non-critical cases, as well as in-hospital mortality in critical cases.
Li Huiqing	Patients with newly diagnosed diabetes had the highest percentage to be admitted to the ICU (11.7%) and require IMV (11.7%), followed by patients with known diabetes (4.1%; 9.2%) and patients with hyperglycemia (6.2%; 4.7%), compared with patients with normal glucose (1.5%; 2.3%), respectively. The multivariable-adjusted HR of mortality among COVID-19 patients with normal glucose, hyperglycemia, newly diagnosed diabetes, and known diabetes were 1.00, 3.29 [95% CI 0.65, 16.6], 9.42 [95% CI 2.18, 40.7], and 4.63 [95% CI 1.02, 21.0], respectively

FBG: Fasting Blood Glucose.
T2DM: Type 2 Diabetes.
ICU: Intensive Care Unit.
IMV: Invasive Mechanical Ventilation.
OR: Odds Ratio.
RR: Risk Ratio.
HR: Hazard Ratio.

Finally, in the systematic review and dose-response meta-analysis involving 14.502 COVID-19 patients, Lazarus et al. have successfully shown robust evidence on the association between FBG and COVID-19 severity and moderate evidence on mortality and poor outcomes [64]. The finding of selected studies on blood glucose level in COVID-19 is summarized in Table 3.

5.3. Antidiabetic agents

Careful selection of glucose-lowering medication in COVID-19 infection is crucial as several glucose-lowering agents may influence the efficiency of immune system in combating the infection. Patients' clinical status and organ function have to be considered as several glucose-lowering medications might not be suitable for severe sepsis or severe impairment of hepatic and renal function [65]. Metformin is one of the most utilized glucose-lowering agents, exerts anti-inflammatory actions, and reduces circulating inflammatory biomarkers in patients with T2DM [66,67].

However, there is scarcity of information regarding the effect and interactions of metformin in coronavirus infections. Although there are some evidence regarding the favourable effect of metformin in patients with COVID-19, the certainty of evidence is weak because the data were observational in nature. This uncertainty leads to no warrant for the use of metformin, especially in patient with severe hepatic and renal impairment [65].

Dipeptidyl peptidase-4(DPP4) inhibitor is a commonly used glucose-lowering agent in patients with T2DM [65]. DPP4 is a widely expressed cell surface endopeptidase that interacts with cellular proteins and generates intracellular signaling for the immune system [68]. DPP4 also regulates the expression of several chemokines and serves as a marker of activated T lymphocytes [69–71]. Both ACE2 and DPP4 is shed from the cell membrane and may circulate while retaining its catalytic actions [72].

The possibility of increased viral infection due to the DPP4 inhibition raised some concerns. Fortunately, DPP4 inhibitors do not seem to alter the circulating leukocyte. One study showed no significant differences in terms of leukocytes percentage and plasma chemokine/cytokine levels after 28 days of sitagliptin administration compared to the control group [73]. In another study, there was no direct association between the use of DPP4 inhibitors and risk of community-acquired pneumonia in patients with diabetes [74,75]. Another interesting finding is the possibility of SARS-CoV2 binding to either DPP4 surface receptor or soluble DPP4, even though the role of soluble DPP4 in viral clearance is uncertain [76,77]. Up until date, the use of DPP4 inhibitor is not associated with worse outcome, and the possibility of alteration in the viral receptors, the T cell functions or even the improvement of clinical outcomes in patients with COVID-19 remain inconclusive, and further studies are needed [15,25,65,78–81].

The use of glucagon-like peptide 1 (GLP1) analogue is known to reduce the major cardiovascular complications in T2DM patients [82]. Aside from the glucose lowering effect, GLP1 reduces the accumulation of monocyte to various tissues and regulate the inflammation in macrophage, therefore attenuating atherosclerosis [83]. One study demonstrates the IL-6 lowering effect of GLP1 infusion in patients with T1DM [84]. Preserving the cardiovascular and renal function is both essential and challenging in patients with COVID-19, as both pre-existing chronic conditions are prevalent in patients with DM. Glucagon-like peptide 1 (GLP1) analogue is known to reduce major cardiovascular complications in T2DM patients and has anti-inflammatory effect which may be useful for tailored diabetes management in patients with COVID-19 [82,85].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are commonly used to treat T2DM, mainly acting on the kidney SGLT2 to reduce blood sugar levels. SGLT2 inhibitors are known to reduce inflammatory cells infiltration into arterial plaque and modulate the mRNA expression of certain cytokines such as IL-6 and tumor necrosis factor (TNF) [86,87]. The cardioprotective effect in the context of heart failure is one major

advantage related to the use of SGLT2 [65]. However, the use of SGLT2 inhibitors in critically ill patients is not without risks.

Administration of SGLT2 inhibitors might be limited in critically ill patients as the fluid status of the patients has to be monitored closely. The use of SGLT2 inhibitors might cause osmotic diuresis that may lead to dehydration and hemodynamics alteration [65,88]. Another limitation in using SGLT2 inhibitors is the patient's glomerular filtration rate which is typically reduced during the critical period, and therefore the glucose-lowering effects will be limited in these patients. Euglycemic ketoacidosis might also develop as a consequence of the use of SGLT2 inhibitors [88].

Another potential glucose-lowering agent in modulating inflammatory and oxidative stress has been proposed. Thiazolidinedione exerts its glucose-lowering effect by acting on the nuclear receptor that regulates glucose and lipid metabolism [89,90]. It is proposed that the effect of thiazolidinedione on lowering insulin resistance in the liver and muscle is mainly mediated by modulating the endocrine signaling pathway in adipose tissue [89]. However, weight gain and edema are potential side effects of thiazolidinedione which is unfavorable in patients with a history of heart failure [91]. To date, the use of thiazolidinedione in patients with COVID-19 is still limited and needs further research.

The role of insulin for hospitalized COVID-19 patients with DM or hyperglycemia is controversial [62,92,93]. In one study, T2DM patients with COVID-19 who received insulin were at increased risk of death, even after propensity matching analysis (aHR of 5.38 and 3.21, respectively) [92]. Nevertheless, residual confounders could not be ruled out, and those who received insulin were generally sicker and has higher glucose levels that requires insulin use in the first place. Additionally, it is unlikely that this hypothesis will be tested in future randomized controlled trials due to ethical issues [18].

Taken in sum, of all agents that are mentioned above, prudent selection of glucose-lowering agents is salient. As a consequence of the precipitating infection, acute hyperglycemia should be anticipated, and rapid blood sugar control should be achieved. Vague evidence regarding insulin should not deter its use in hospitalized patients requiring tight glucose control. The finding of selected studies on antidiabetic drugs is summarized in Table 4.

Table 4
Antidiabetic drugs on outcome.

Author	Summary of findings
Noh Y	In the adjusted model, DPP4 inhibitor use was insignificantly associated with all-cause mortality (HR 0.74 [95% CI 0.43, 1.26]) and severe manifestations (HR 0.83 [95% CI 0.45, 1.53]) compared with the reference group.
Solerte BS	Treatment with sitagliptin at the time of hospitalization was associated with reduced mortality (18% vs. 37% of deceased patients; HR 0.44 [95% CI 0.29, 0.66]; p = 0.0001), with an improvement in clinical outcomes (60% vs. 38% of improved patients; p = 0.0001) and with a greater number of hospital discharges (120 vs. 89 of discharged patients; p = 0.0008) compared with patients receiving standard of care
Mirani, M	risk of mortality was significantly associated with a history of hypertension (adjusted HR [aHR] 1.84 [95% CI 1.15, 2.95]; p = 0.011), coronary artery disease (aHR 1.56 [95% CI 1.04, 2.35]; p = 0.031), chronic kidney disease (aHR 2.07 [95% CI 1.27, 3.38] p = 0.003), stroke (aHR 2.09 [95% CI 1.23, 3.55]; p = 0.006), and cancer (aHR 1.57 [95%CI 1.08, 2.42; p = 0.04]) but not with T2DM (p = 0.170).
Zhou JH	There was no significant association between in-hospital DPP4 inhibitor use and 28-d all-cause mortality (adjusted HR = 0.44, 95% CI: 0.09–2.11, p = 0.31).
Yu, B	Insulin treatment for patients with COVID-19 and T2D was associated with a significant increase in mortality (27.2% versus 3.5%; aHR5.38 [2.75–10.54]).

DPP4: Dipeptidyl peptidase 4.
HR: Hazard Ratio.
aHR: adjusted Hazard Ratio.
CI: Confidence Interval.
T2DM: Type 2 Diabetes.

6. Acute diabetes complications

Pancreatic involvement in patients with COVID-19 is plausible because pancreatic injury was reported in hospitalized COVID-19 patients. Pancreatic injury was defined as increased amylase and lipase. Among 52 patients, 9/52 and 6/52 were found with pancreatic injury and elevated glucose levels, respectively [94]. Whether the acute hyperglycemia was due to pancreatic injury alone or as a part of complex interplay between other possible mechanisms remain inconclusive.

Attention is now directed towards the increased frequency and severity of acute life-threatening complications associated with diabetes in hospitalized patients, which is suspected due to COVID-19 potential diabetogenic effect [95]. A cohort study conducted in the United States of America, which includes 5029 patients with diabetic ketoacidosis (DKA), has several notable findings in the differences of clinical characteristics between patients with COVID-19 and without COVID-19 that might bring some critical clues. From the perspective of age, patients with COVID-19 tend to be older than patients without COVID-19 (56 $\pm$ 17 years vs. 47 $\pm$ 18 years; p $\leq$ 0.001) [96]. Another finding in patients with COVID-19 has a higher body mass index in comparison to patients without COVID-19 (31 $\pm$ 9 kg/m^2 vs 28 $\pm$ 8 kg/m^2; p $\leq$ 0.001) [96]. Mortality and daily insulin dose are also higher in the patients with COVID-19 than patients without COVID-19 [96]. These findings may suggest possible interactions between the diabetogenic effect of COVID-19, obesity, and inflammatory response generated by the infection in the context of acute life-threatening complications of diabetes [96]. However, despite all of the findings, the exact mechanism remains unknown, and appropriate care needs further studies to be elucidated [96]. The project of CoviDIAB is a registry made by a group of global leading diabetes researchers that might shed light on the extent and phenotype of new-onset diabetes in COVID-19 patients and gain knowledge in giving appropriate inpatient care with both conditions of COVID-19 and diabetes [95].

Potential causes of acute deterioration of glycemic control in diabetic patients during infection are hypothesized as follows [97]. Firstly, chronic inflammation and hyperglycemia in diabetic patients may provide a worse baseline in comparison to non-diabetic patients. Secondly, acute inflammatory response further provokes insulin resistance [98–100]. Thirdly, obesity which is prevalent in patients with diabetes may further promote insulin resistance. Lastly, SARS-CoV2 might directly alter pancreas function and might cause impairment in insulin secretion. (Fig. 1) Potential mechanism of blood glucose dysregulation in diabetic patients with COVID-19.)
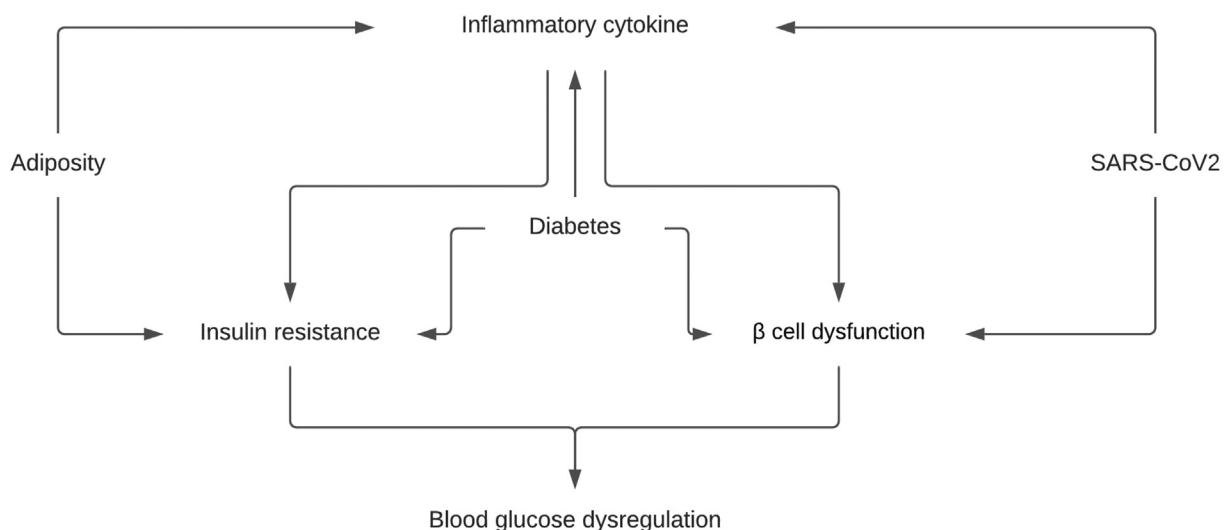
7. Vaccinating diabetes communities

Even though there is no solid evidence that proves increased susceptibility to COVID-19 in patients with diabetes, vaccination should be prioritized in patients with diabetes due to the higher risk of severe COVID-19 and its associated complications. Concerns regarding the poor immunological response of patients with DM, as seen previously in Influenza or Hepatitis B vaccine, may not be the case in COVID-19 [101].

Dispinseri et al. showed that anti SARS-CoV-2 neutralizing antibodies' (Nabs) kinetic and durability were not affected by diabetes/hyperglycemia status. More importantly, Nabs positivity at the time of hospital admission conferred a protective effect, independent of diabetes status (HR 0.28, p = 0.046 (with diabetes), HR 0.26, p = 0.030 (without diabetes) [102].

Another prospective observational study of 509 patients with documented COVID-19 (139 patients with DM; 90 with pre-existing diabetes and 49 newly diagnosed diabetes) demonstrated that COVID-19 patients with DM had a comparable humoral response to those without DM and were not affected by glucose levels. Likewise, IgG to SARS-CoV-2 receptor binding domain conferred protective effect independent of diabetes status (HR 0.37, p = 0.013 (with diabetes), HR 0.43, p = 0.038 (without diabetes)) [103]. There was a lack of study that addresses the mechanistic basis that may alter immunological response in patients with diabetes receiving vaccination. In sum, the immunological response of patients with DM will likely be comparable to non-DM patients.

Another issue is regarding vaccine rollout prioritization. Initially, the Centers for Disease Control and Prevention (CDC) put patients with T2DM at higher risk for severe COVID-19 outcomes than T1DM, major medical societies urged that both groups should be prioritized equally. Others have argued that younger patients with DM should be prioritized early for vaccine rollout because they "disproportionately impacted in terms of life years lost and are of working age, which puts them at potentially higher risk of exposure, alongside the excess relative COVID-19 mortality risk in younger people with diabetes" [104]. CDC has since then, prioritized T1DM and T2DM equally for vaccination. Thus, in light of the available evidence, COVID-19 vaccination should be prioritized early for DM patients, irrespective of age or type of diabetes.

8. Post pandemic era

The implementation of lockdown and travel restrictions requires attention since the delivery of generalized and specialized medical services is limited [105]. Patients with chronic non-communicable diseases, such as DM and its associated complications, are at risk, since

Fig. 1. Potential mechanism of blood glucose dysregulation in diabetic patients with COVID-19.

their routine medical follow-up schedule is affected due to the restrictions. These patients are at risk of both adverse outcomes and more severe COVID-19 since physical inactivity might seem to be related to their well-being and without access to routine medical care [4,106–110]. Previous SARS-CoV outbreak has shown a possibility of long-lasting metabolic alteration, which may predispose patients to cardiovascular diseases [111]. Therefore, the surge of non-communicable diseases has to be anticipated by implementing new strategies to advance health-related technologies and telemedicine [109].

9. Conclusions

Diabetes is a prevalent chronic disease that is independently associated with poor outcomes in COVID-19 patients. Thus, appropriate interventions are needed to mitigate the increased risk faced by this population. With vaccines available, vaccinating this population is the crucial first step. Then, DM management should focus on BG control related to the patient's outcome. With the help of telemedicine and rCGM, this goal should be achieved.

Moreover, several antidiabetic agents are also revisited due to their immunomodulating properties, which is vital in combating COVID-19 associated hyperinflammatory syndrome. Importantly, patients from underserved communities should be addressed as they are

disproportionately affected. Lastly, this review never meant to be exhaustive, as gaps in the topics exist, and future research and findings will help fill in (Fig. 2).

Fig. 2. Patients with COVID-19 and diabetes mellitus: risk mitigation strategies.
Legend: Patients with COVID-19 and diabetes mellitus are at increased risks for poor composite outcomes. Therefore, risk mitigation strategies are essential. The red dash lines are the protective effect of these strategies on this population. T1D: type 1 diabetes mellitus, T2D: diabetes mellitus, SARS-CoV-2: Severe acute respiratory syndrome-Coronavirus-2, COVID-19: coronavirus disease 2019, BGs: Blood glucose levels, CGM: continuous glucose monitoring. * as explained in the respective subheading.

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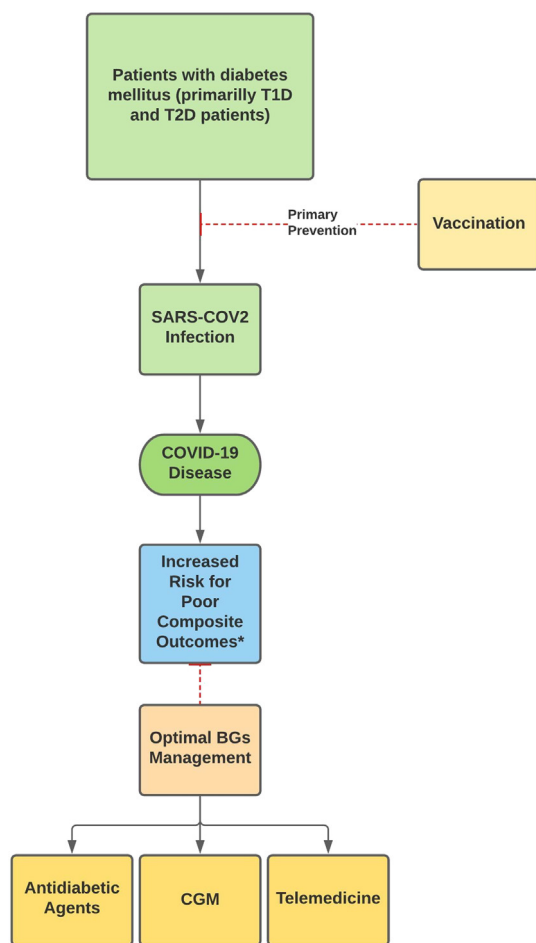
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