Glucometabolic Perturbations in Type 2 Diabetes Mellitus and Coronavirus Disease 2019: Causes, Consequences, and How to Counter Them Using Novel Antidiabetic Drugs – The CAPISCO International Expert Panel

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ABSTRACT

The growing amount of evidence suggests the existence of a bidirectional relation between coronavirus disease 2019 (COVID-19) and type 2 diabetes mellitus (T2DM), as these two conditions exacerbate each other, causing a significant healthcare and socioeconomic burden. The alterations in innate and adaptive cellular immunity, adipose tissue, alveolar and endothelial dysfunction, hypercoagulation, the propensity to an increased viral load, and chronic diabetic complications are all associated with glucometabolic perturbations of T2DM patients that predispose them to severe forms of COVID-19 and mortality. Severe acute respiratory syndrome coronavirus 2 infection negatively impacts glucose homeostasis due to its effects on insulin sensitivity and β-cell function, further aggravating the preexisting glucometabolic perturbations in individuals with T2DM. Thus, the most effective ways are urgently needed for countering these glucometabolic disturbances occurring during acute COVID-19 illness in T2DM patients. The novel classes of antidiabetic medications (dipeptidyl peptidase 4 inhibitors (DPP-4is), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium-glucose co-transporter-2 inhibitors (SGLT-2is) are considered candidate drugs for this purpose. This review article summarizes current knowledge regarding glucometabolic disturbances during acute COVID-19 illness in T2DM patients and the potential ways to tackle them using novel antidiabetic medications. Recent observational data suggest that preadmission use of GLP-1 RAs and SGLT-2is are associated with decreased patient mortality, while DPP-4is is associated with increased in-hospital mortality of T2DM patients with COVID-19. Although these results provide further evidence for the widespread use of these two classes of medications in this COVID-19 era, dedicated randomized controlled trials analyzing the effects of in-hospital use of novel antidiabetic agents in T2DM patients with COVID-19 are needed.

Introduction

Diabetes mellitus (DM) represents one of the major risk factors for more severe forms and mortality of coronavirus disease 2019 (COVID-19) infection, an ongoing pandemic that has a dramatic impact on global well-being [1, 2]. There is now enough evidence to suggest that individuals with DM are at a higher risk of developing COVID-19-related complications, notably intensive care unit (ICU) admission and death [3–7].

On the other hand, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, is a risk factor for compromised glycemic control, the acute metabolic complications associated with severe hyperglycemia among individuals with previously diagnosed DM, as well as new-onset diabetes [8, 9].

The growing amount of evidence suggests the existence of a bidirectional relation between COVID-19 and type 2 DM (T2DM) [10, 11]. Indeed, these two conditions aggravate each other, causing a significant healthcare and socioeconomic burden [12]. This review article aimed to summarize current knowledge regarding glucometabolic disturbances during acute COVID-19 illness in T2DM patients and the potential ways to tackle them using novel antidiabetic medications.

Methods

We performed an electronic search in PubMed, Google Scholar, and SCOPUS databases in order to identify so far published studies using various combinations of the following keywords: "angiotensin-converting enzyme 2, coagulation, coronavirus disease 2019, COVID-19, dipeptidyl peptidase 4 inhibitors, endothelial function, glucagon-like peptide 1 receptor agonists, glycemic control, hyperglycemia, immunity, inflammation, in-hospital, insulin resistance, insulin secretion, insulin sensitivity, mechanical ventilation, mortality, new-onset diabetes, outcomes, outpatient, preadmission, pulmonary function, severity, sodium-glucose co-transporter 2 inhibitors, type 2 diabetes mellitus, β-cell function, and β-cell death". Only publications in the English language were considered.

Perturbations associated with type 2 diabetes mellitus and COVID-19 outcomes

Epidemiological data have shown that individuals with both type 1 DM and T2DM are at increased risk of ICU admission and death from COVID-19 compared to the background population [13, 14].

Numerous mechanisms linking DM to worse COVID-19 outcomes have been proposed so far.

In general, subjects with T2DM are characterized by impaired immune function with defects in both innate and adaptive cellular immunity. The most specific alterations of innate immunity associated with T2DM and obesity are the reduced activity of natural killer cells and the increased proinflammatory phenotype of adipose tissue macrophages [15]. As far as adaptive cellular immunity is concerned, T2DM is characterized by the overactivation of T cells and inflammatory pathways. It has been reported that T cells are abnormally differentiated in individuals with T2DM, which leads to an elevation in the levels of different circulating cytokines. All these immunological perturbations promote low-grade chronic inflammation in T2DM [15].

In the event of SARS-CoV-2 infection in subjects with T2DM, delayed interferon-γ response and prolonged inflammation may lead to more severe disease, exacerbating the cytokine storm [15, 16]. The latter represents a life-threatening systemic inflammatory syndrome involving elevated circulating cytokine levels and immune cell hyperactivation, which can be triggered by various pathogens, autoimmune conditions, monogenic disorders, cancers, and different therapies. This results in an imbalance in cytokine production intended to eliminate the invading agent, leading to a hyperinflammatory response and clinically significant collateral damage [17]. In addition, chronic hyperglycemia downregulates the expression of angiotensin-converting enzyme 2 (ACE2), the main entry receptor for SARS-CoV-2, rendering cells very vulnerable [18].

Among several molecules, glucose-regulated protein 78 (GRP78), also known as immunoglobulin heavy chain binding protein, is receiving continuous attention in research [19]. It has a signal peptide sequence that acts as a molecular chaperone on the endoplasmic reticulum [19]. GRP78 has a critical role in protein folding functions and is overexpressed and translocated to the cell surface under stressed conditions, serving as a receptor for various endogenous and exogenous ligands [20]. Clinical data suggest that GRP78 levels are significantly increased in COVID-19 patients [21–23]. Molecular docking analyses have pointed out a putative interaction between GRP78 and the receptor-binding domain of the SARS-CoV-2 spike protein [24]. Additionally, GRP78 is a promoter of SARS-CoV-2-spike-ACE2 binding, which also facilitates cell surface ACE2 expression [19]. A recent experimental study has confirmed that SARS-CoV-2 spike protein interacts with cell surface GRP78 and has also shown that GRP78 is highly expressed in adipose tissue, especially in the case of old age or DM [25].

Alveolar dysfunction might also be one of the mechanisms linking T2DM to worse COVID-19 outcomes. According to data from the US on hospitalized patients with COVID-19 who died, those with DM were more likely to receive invasive mechanical ventilation in ICU than patients without DM [6]. Further, in T2DM, pulmonary function parameters (forced vital capacity, total lung capacity, alveolar membrane permeability, and alveolar gas exchange) are often significantly reduced [26], while the endothelial capillary basal lamina and alveolar epithelia may be thicker [27].

SARS-CoV-2 infection can also initiate endothelial cell injury [28]. Conversely, endothelial dysfunction is a hallmark of DM, which is mainly caused by the impact of hyperglycemia on the endothelium integrity. Both acute and long-term hyperglycemia impact levels of sorbitol, protein kinase C, and the pentose phosphate pathway, and cause the decreased availability of nitric oxide, which all contribute to the development of endothelial dysfunction [29]. This chronic endothelial dysfunction is associated with an increase in leukocyte adhesion, vascular permeability, and coagulation [30, 31]. Consequently, endothelial dysfunction in T2DM may contribute to cytokine storm development and multiple organ lesions during acute COVID-19 illness.

COVID-19 can also activate coagulation. For instance, more severe forms of COVID-19 are associated with hypercoagulation, elevated levels of D-dimer, and fibrin/fibrinogen degradation products. There is also a significantly increased risk of deep vein thrombosis and pulmonary embolism [32]. Given that subjects with DM carry an increased risk of excessive inflammation, they may be at a greater risk of experiencing coagulation abnormalities during COVID-19 infections. Of note, hyperglycemia exacerbates coagulation, while hyperinsulinemia attenuates fibrinolytic activity [33, 34]. All these findings might explain the increased risk of COVID-19-associated thromboembolic events in T2DM patients.

Subjects with DM might also be exposed to an increased SARS-CoV-2 viral load. A study showed that hyperglycemia increases SARS-CoV-2 replication and viral load [35]. Increased viral replication is enabled by increased mitochondrial reactive oxygen species production and activation of hypoxia-inducible factor 1α in monocytes, resulting in T-cell dysfunction [35]. Furthermore, obesity and hyperinsulinemia could lead to an increased SARS-CoV-2 viral load in T2DM due to the viral impact on the increased expression of ACE2 [36]. Interestingly, ACE2 documented an increased expression in various organs in DM animal models [37]. Further, some antidiabetic agents (glucagon-like peptide-1 receptor agonists [GLP-1 RAs]), ACE inhibitors, and statins could increase its expression [38].

Additionally, the presence of microvascular and macrovascular complications has been shown to be responsible for worse COVID-19 outcomes and higher rates of mortality in T2DM patients [13, 14, 39].

Glucometabolic perturbations during acute COVID-19

Importantly, COVID-19 affects glucose homeostasis even in people without DM. There are several underlying mechanisms implicated. Definitely, systemic corticosteroids, antiviral agents, and other drugs often used to treat COVID-19 may aggravate hyperglycemia [28, 40, 41]. Moreover, SARS-CoV-2 infection impairs the sensitivity of target tissues to insulin [42]. It also leads to the overactivation of angiotensin II, resulting in the lowering of insulin sensitivity, hyperinsulinemia with increased oxidative stress, and inflammatory response [43]. Insulin resistance and inflammation have a bidirectional relationship, aggravating each other and jointly initiating β-cell hyperstimulation and apoptosis [42]. Conversely, increased angiotensin II activity also induces hypersecretion of aldosterone and potassium loss, which further lowers insulin secretion [44].

Several possible underlying mechanisms can explain the acute pancreatic β-cell dysfunction caused by SARS-CoV-2. The inflammatory response caused by infection could cause a cytokine-

mediated detrimental effect on the β-cell capacity to adequately sense glucose and secrete insulin [28].

However, SARS-CoV-2 itself might also have direct harmful effects on β-cells. Previous studies with severe acute respiratory syndrome coronavirus 1 point out that it may cause β-cell damage, given that a high glucose level persists up to three years after recovery from the Severe Acute Respiratory Syndrome [45]. Importantly, ACE2 is expressed in β-cells [46]. After binding to the ACE2 receptor, SARS-CoV-2 enters host cells, followed by internalization of both SARS-CoV-2 and ACE2 by endocytosis, leading to ACE2 receptor downregulation [43]. It has been postulated that lowered ACE2 expression leads to inflammatory injury of pancreatic β-cells [47, 48]. This hypothesis has been confirmed in preclinical settings. For example, in high-fat diet conditions, ACE2 knockout mice had a higher percentage of dedifferentiated β-cells [49], as well as a higher susceptibility to develop β-cell dysfunction compared with wild-type mice [50]. Additionally, ACE2 deletion in non-obese diabetic mice was associated with hyperglycemia, β-cell oxidative stress, and diminished insulin secretion [51]. Experimental evidence has also shown that β-cell ACE2 expression resulted in SARS-CoV-2 tolerance, culminating in cytokine inflammation, β-cell apoptosis, and reduced insulin secretion [52]. Autopsy studies have demonstrated that SARS-CoV-2 infected pancreatic β-cells and could lead to either their death or trans-differentiation [53, 54]. The presence and replication of SARS-CoV-2 in pancreatic islets, accompanied by insulin-secretory granule reduction, has been confirmed in one study employing human islet cell cultures and full-body postmortem material after COVID-19 infection [55].

However, SARS-CoV-2 entry is considered to be mediated not only by ACE2 but also by transmembrane serine protease 2, neuropilin 1, and transferrin receptor, which are all expressed in pancreatic β-cells [53]. Among these, ACE2 remains a crucial factor for understanding β-cell impairment during COVID-19 [28]. Chronic hyperglycemia downregulates ACE2 expression, thereby increasing the severity of SARS-CoV-2 infection and causing damage in pancreatic β-cells and other cells with ACE2 expression [18, 47, 48]. However, unlike chronic hyperglycemia, acute hyperglycemia appears to trigger ACE2 expression, which leads to increased ACE2 urinary activity [28]. Increased urinary ACE2 to creatinine levels were found in T2DM compared with healthy subjects that were positively correlated with fasting blood glucose and glycated hemoglobin levels [56]. Thus, the role of ACE2 in β-cell function impairment during COVID-19 needs to be further studied.

Finally, although it was speculated that SARS-CoV-2 might also enter cells by binding to dipeptidyl peptidase 4 (DPP-4), studies in this regard are still showing conflicting results [47, 57, 58].

Novel antidiabetic drugs and their impact on glucometabolic perturbations during acute COVID-19

There is a growing interest in the role of antidiabetic treatment, particularly in the novel classes of antidiabetic agents (DPP-4 inhibitors (DPP-4is), GLP-1 RAs, and sodium-glucose co-transporter-2 inhibitors (SGLT-2is) for the management of hyperglycemia in people affected by COVID-19 [59–61]. Although previous studies showed controversial results, as we have already described earlier [62], a recent meta-analysis comparing the effects of the preadmission use of different antidiabetic drugs on in-hospital mortality of 3,061,584 T2DM patients with COVID-19 provides more robust evidence in this regard [63].

Dipeptidyl peptidase 4 inhibitors

There have been speculations that SARS-CoV-2 might enter cells by binding to DPP-4 [47, 57, 58]. Therefore, it has been suggested that DPP-4is could be of therapeutic benefit in T2DM patients with COVID-19. Furthermore, this notion has been corroborated by other potential beneficial actions of DPP-4is in COVID-19 patients. First, DPP-4 promoted cell proliferation, CD86 expression, and activation of the nuclear factor kappa-light-chain enhancer of the activated B cell signaling pathway, which resulted in the excessive production of inflammatory cytokines [64, 65]. Sitagliptin reduced the levels of some of these inflammatory cytokines [66, 67]. Indirect beneficial properties could also be seen as the mechanism of action is based on the inhibition of endogenous GLP-1 degradation, thus potentiating the anti-inflammatory actions [68]. Theoretically, all of these postulated mechanisms could attenuate numerous inflammatory-induced events. Additionally, inhibition of endogenous GLP-1 degradation may protect β-cell function, proliferation, differentiation, and survival [69].

However, studies on the impact of DPP-4is on COVID-19 outcomes have shown diverse and very inconsistent results [62]. Surprisingly, a previously mentioned meta-analysis demonstrated that only insulin (odds ratio [OR]: 1.70; 95 % confidence interval [CI]: 1.33–2.19) and DPP-4is (OR: 1.23; 95 % CI: 1.07–1.42) preadmission use were associated with increased in-hospital mortality of T2DM patients with COVID-19 [63]. Arguably, such higher mortality rates in DPP-4is users should be cautiously interpreted because they tend to be more frequently used among older fragile people and those with comorbidities. Nevertheless, subgroup analyses showed that DPP-4is might have little or no benefit among groups differed by vulnerability, suggesting that DPP-4is might not be associated with favorable COVID-19 outcomes [63]. Thus, despite the initial enthusiasm, DPP-4is usage may not be ideal in addressing glucometabolic perturbations during acute COVID-19 and in reducing disease severity and mortality.

Glucagon-like peptide-1 receptor agonists

Endogenous GLP-1 has been shown to possess important anti-inflammatory properties that are beyond the scope of this review [68, 70]. In terms of SARS-CoV-2 infection, liraglutide was shown to activate ACE2 expression in experimental animals [71], but the significance of this action is not fully elucidated. It has been demonstrated that, in T2DM patients, liraglutide administration reduced oxidative stress [72], which represents one of the main pathophysiological events responsible for the development of glucometabolic perturbations and more severe forms of COVID-19 in T2DM patients. Definitely, the effects of GLP-1 on the β-cell mass are yet another possible mechanism in countering glucose homeostasis defects arising during COVID-19 [69]. Eventually, the results of an ongoing trial (NCT04615871) analyzing whether semaglutide can reduce mortality or the need for mechanical ventilation in a broad elevated-risk COVID-19 population requiring hospitalization (with any two of the high-risk features including older age,

obesity, DM, hypertension, established atherosclerotic cardiovascular disease, chronic kidney disease, elevated admission troponin or D-dimer, and decreased oxygen saturation) will further elucidate the effect of GLP-1 RAs on the COVID-19 outcomes.

Although previous studies suggested that GLP-1RAs are likely to have beneficial effects on COVID-19 outcomes, the data were not robust enough [62]. The already mentioned meta-analysis showed that metformin (OR: 0.54; 95 % CI: 0.47–0.62), SGLT-2is (OR:0.60; 95 % CI: 0.40–0.88), and GLP-1RAs (OR: 0.51; 95 CI %: 0.37–0.69) preadmission usage was associated with decreased in-hospital mortality of T2DM patients with COVID-19 [63]. Given their beneficial metabolic and cardiorenal effects [73], it is not surprising that GLP-1RAs may exert some positive effects in the context of COVID-19 severity. However, the initiation and maintenance of their administration in critically ill patients are not fully recommended, because they require slow titration and time to become effective, and they are often associated with transient gastrointestinal side effects [40]. Finally, their beneficial effects might be less pronounced in vulnerable patients with COVID-19 [63].

Sodium-glucose co-transporter-2 inhibitors

Although SGLT-2is could indirectly promote ACE2 activity [74] to facilitate viral cell entry, they may also decrease it by raising the cytosolic pH [75]. In patients with T2DM, treatment with SGLT-2is led to a decrease in messenger ribonucleic acid levels of some cytokines and chemokines (such as tumor necrosis factor alpha-α, interleukin-6, and monocyte chemoattractant protein 1), resulting in reduced inflammation [76]. Additional pleiotropic effects of SGLT-2is include down-regulation of oxidative stress, amelioration of endothelial dysfunction, and increased concentrations of erythropoietin, which in theory could protect against the vascular and cardiorenal complications of COVID-19 [77]. However, some of the early reports pointed out that SGLT-2is did not improve COVID-19-related severe pneumonia among patients without DM [78].

More recently, it has been hypothesized that dapagliflozin could decrease lactic acidosis and reverse cellular acid-base balance during hypoxia, thus contributing to the prevention of cell injury during the cytokine storm in COVID-19 illness among T2DM patients [79]. Therefore, the Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19) trial aimed to analyze if the cardio- and renoprotective benefits of dapagliflozin could be extrapolated to high-risk patients with COVID-19 with at least one cardiometabolic risk factor (hypertension, T2DM, atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease) but not critically ill, has been conducted [80]. The investigators assessed the time to development of new or worsened organ dysfunction, or all-cause mortality, the composite endpoint of change in clinical status through day 30, as well as the safety of dapagliflozin. However, the trial results did not reach statistical significance for the primary endpoints of prevention of organ dysfunction, reduction in all-cause mortality, and improvement in clinical status (ranging from early recovery to death) at 30 days [80]. The study was designed and carried out in the course of an evolving pandemic, during which the treatment of patients with COVID-19 presented continuous improvement; therefore, the exact estimate of the numbers required to achieve statistical significance was challenging [81]. Several other ongoing trials assessing the impact of SGLT-2is therapy on COVID-19 outcomes among patients requiring hospitalization (NCT04393246, NCT04505774, and NCT04381936) should provide the deepest insight into their potentially beneficial effects in this regard.

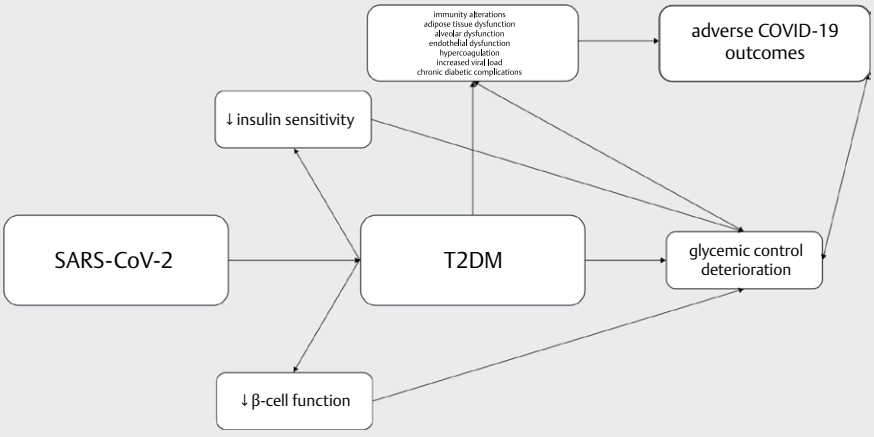
Ultimately, due to their insulin-independent manner of action, SGLT-2is protects β-cells against glucose toxicity and preserves insulin secretory capacity [82], which could be of great importance during acute COVID-19 illness.

Initially, studies on the impact of SGLT-2is on COVID-19 outcomes were not consistent [62], but a recent large-scale meta-analysis has demonstrated that SGLT-2is preadmission use was associated with decreased in-hospital mortality of T2DM patients with COVID-19, especially in those with high baseline body-mass index or chronic kidney disease [63]. This has encouraged the hope that SGLT-2is may favorably impact COVID-19 severity and mortality. However, their practical use might be complicated, especially among those requiring critical care, due to the risk of dehydration, diabetic ketoacidosis, and acute kidney injury [40, 83]. The risk of euglycemic diabetic ketoacidosis is increased due to: a) volume depletion caused by vomiting and anorexia; b) the direct effect of SARS-CoV-2 on β-cells leading to reduced endogenous insulin secretion and the increased inflammatory response [84]. On the other hand, in the DARE-19 study, severe adverse events were numerically fewer in the intervention compared to the placebo arm. There were only two cases of ketoacidosis in patients treated with dapagliflozin that resolved rapidly with appropriate treatment. The use of SGLT2-is in the context of acute disease has been considered prohibitive for many years. However, in light of the reassuring findings of DARE-19 showing that the risks are mitigated with proper selection and close follow-up of the patients, a recent consensus of an international expert panel calls for reexamining the widespread policy of stopping SGLT2-is during acute illness and asks for more research in this area [85]. Anyhow, their favorable effects might be less prominent in vulnerable COVID-19 patients [63].

Conclusions

Evidence points to a bidirectional relationship between COVID-19 and T2DM. T2DM is a major risk factor for more severe forms and mortality of COVID-19. Conversely, COVID-19 is associated both with impaired glycemic control in T2DM and with new-onset diabetes. The various glucometabolic perturbations of T2DM are greatly responsible for the more severe COVID-19 forms, while the infection itself further exacerbates them (▶ **Fig. 1**). The potential favorable effects of novel antidiabetic agents (DPP-4is, GLP-1RAs, and SGLT-2is) on COVID-19 outcomes have been studied during the last 2 years.

Previous reports on such beneficial effects of these antidiabetic agents have not been consistent, although data on GLP-1RAs and SGLT-2is showed promising results [62]. However, a recent large meta-analysis demonstrated that while the preadmission use of GLP-1RAs and SGLT-2is was associated with decreased in-hospital mortality of T2DM patients with COVID-19, the preadmission use of DPP-4is was associated with increased COVID-19 fatality [63]. Although these results encourage the use of these two classes of antidiabetic agents, they are limited to their pre-COVID-19 administration. Thus, randomized controlled trials need to examine the



▶ **Fig. 1** Glucometabolic perturbations in type 2 diabetes mellitus and coronavirus disease 2019.; Key: COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; T2DM: type 2 diabetes mellitus.

effects of these agents when used in hospitalized T2DM patients with COVID-19.

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Conflicts of Interest

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