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LITERATURE REVIEW

Use of Insulin during the Current Pandemic

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Abstract

Insulin is one of the greatest medical discoveries of the twentieth century and it continues to be the solitary effective treatment for type 1 diabetes mellitus patients and save millions of lives around the world. In 2021, we have rejoiced 100 years of insulin discovery. The COVID-19 pandemic is currently the most threatening to the global health system, the management of patients with endocrine disorders during this pandemic stance has exceptional challenges. Diabetic patients are prone to more severe illness if infected by COVID-19 and the virus seems to prompt acute demonstration of Diabetes Mellitus (DM) which includes Hyperosmolar Hyperglycemic State (HHS), Diabetic Ketoacidosis (DKA), and serious resistance to insulin. Researchers are currently investigating further details of the impact of COVID-19 on the use of insulin for diabetic patients and developing guidelines for the management of complications related to DM. In this article, we aim to give a comprehensive review of the overall influence of COVID-19 in the use of insulin, its pathophysiological features, its role in the management of patients with hyperglycemia, its clinical outcomes in hospitalized patients, and its contra-indications and side effects based on recent research articles.

Keywords

Insulin, COVID-19, Diabetes mellitus, Hyperglycemia, Insulin resistance, Management

Introduction

Coronavirus 2019 disease is a highly contagious infectious disease mainly affecting the respiratory system, but its inflammatory response and cytokine storm may affect the whole body system [1]. Through mutation, the SARS-CoV-2 virus is posing additional risks to the worldwide population [2,3]. Several risk factors are demonstrated from various observational studies and clinical trials. The ongoing COVID-19 pandemic is a challenge for comorbid patients [4]. Comorbidities increase the severity of COVID-19 and thus increase mortality. This promotes the use of more therapeutics. According to the International Diabetes Federation, approximately 463 million people are living with DM around the globe. Low and middle-income countries are struggling through about 80% diabetic population in the world due to low resources for surveillance and management and the COVID-19 pandemic provoking an overlapping burden in an already crippled health system. Likewise, DM is one of the most important risk factors for concurrent COVID-19 as hyperglycemia has many deteriorating effects on the immune system of our body. The increasing trend of DM is a serious issue in the COVID-19 catastrophe. DM itself is a substantial cause for other morbidities including metabolic syndrome, cardiovascular diseases, kidney disease, etc.

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Therefore, maintaining glycemic control has been an utmost priority in the healthcare system, preventing ICU admission and long hospital stay [5].

A decade has been passed since the discovery of insulin, the greatest tool to fight against DM [6]. The use of insulin therapy lessens the severity by lowering the blood glucose level. However, the prognosis of insulin therapy has been less noticed and studied. Some large-scale cross-sectional study from China has suggested the role of insulin on a COVID-19 patient with diabetes [7]. Moreover, slight modifications of medications may be required in case of co-existing diseases. Similar changes may be required in COVID-19 patients too. Steroids are being used broadly among COVID-19 patients. The use of steroids in severe cases exacerbates the already existing DM and induces new-onset DM [8]. This also compels the use of insulin therapy.

COVID-19 outbreak necessitates a multidisciplinary approach, especially in multimorbid patients. It requires the role of endocrinologists, even more, in collaboration with other specialties. This will hasten the prognosis and prevent the adverse outcomes of COVID-19 patients. Exact data about the association of comorbidity and COVID-19 is still not clear as most available data and studies are from hospital consultation cohorts. However, virtually almost all reports suggest that there is increasing evidence of morbidity and mortality with DM [9]. In addition, DM is the cause of more hospital admissions than in non-diabetics COVID-19 patients. Therefore, the overwhelming use of multiple drugs at a time may be required to manage multiple ongoing problems, but one should be careful about adverse outcomes. In this review, we aimed to culminate the association of the need for insulin use and its impact on the morbidity and mortality of COVID-19 patients.

Pathophysiology

Comorbid DM is not only the second most frequent comorbidity in hospital-admitted COVID-19 infected patients but also the second most important risk factor for developing COVID-19 disease, be it mild or severe. Moreover, diabetes increases the risk of a more severe disease course and mortality. Thus, there is a clear link between diabetes and a worse SARS-CoV-2 infection prognosis. There are many hypothesized mechanisms on how this relationship works. In this review, we explore four of them: The relation of hyperglycemia and COVID-19 infection, inflammation and insulin resistance, the occurrence of typical DM complications in COVID-19 infected patients, and the interaction between SARS-CoV-2, the ACE-2 enzyme, and hyperglycemia [10,11].

Firstly, it was evidenced that the presence of DM type 1 or 2 and hyperglycemia are both independent predictors of mortality and morbidity. This clearly shows that hyperglycemia on its own may negatively modify disease prognosis. Moreover, poorer glycemic control correlates with an increased risk for more therapeutic measures, like medicalization, hospitalization, and an overall increase in mortality. This relationship between higher blood glucose levels and a more severe SARS-CoV-2 infection might be because elevated blood glucose increases SARS-CoV-2 replication [10,11]. This is because a higher glucose level translates into more glycolysis and more glycolysis directly helps SARS-CoV-2 replication by facilitating the production of mitochondrialreactive oxygen species and the activation of the hypoxia-induced factor 1-alpha, a key transcription factor [10,11] (Figure 1).

Secondly, it is common for COVID-19 infected patients to develop severe insulin resistance, thus requiring higher doses of insulin for correct glycemic control. This, translated to a diabetic patient, further deteriorates his/her metabolic control. The reasoning behind this increased insulin resistance is not yet fully understood, but there are two main hypotheses. One

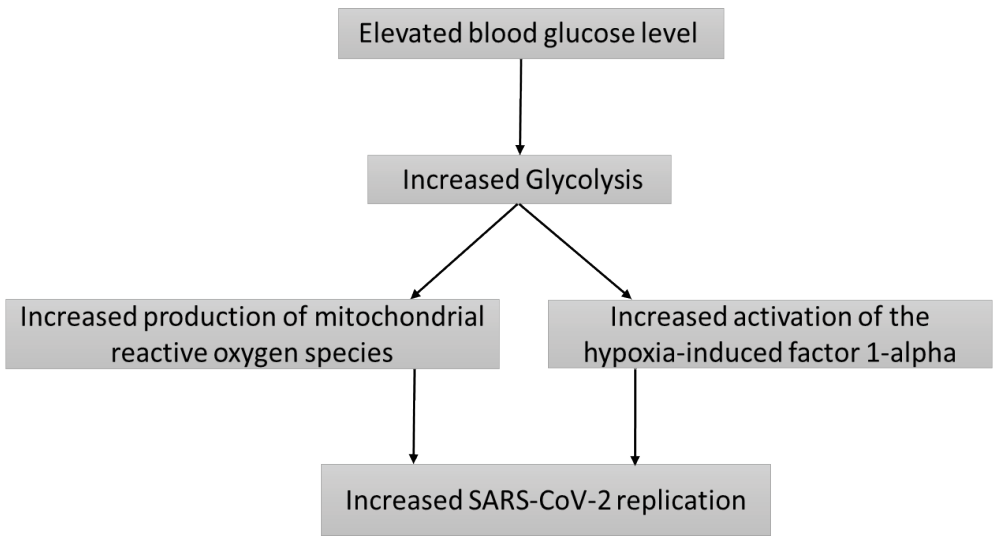

Figure 1: Mechanism of elevated SARS-CoV-2 replication in diabetes mellitus.

states that the systemic increase of inflammatory cytokines (like IFN-gamma and TNF-alpha) secondary to SARS-CoV-2 infection correlates with the level of insulin resistance. It is known that TNF-alpha induces insulin resistance by promoting the activity of protein tyrosine phosphatase 1B that then goes on to dephosphorylate Insulin Receptor Substrate-2 reducing glucose transport across the cell membrane and thus, an increase in serum glycemia [12]. Moreover, IFN-gamma produces insulin resistance by down regulating PI3K (phosphatidylinositol 3 kinase) in adipose and skeletal muscle cells [12].

Thirdly, it is imperative to understand that DM is a chronic disease that is usually associated with a number of life-threatening complications, most importantly cardiovascular heart disease, heart failure, and chronic kidney disease. Patients with these comorbid conditions are at increased odds of suffering further morbidity and mortality [10].

Finally, a key aspect of the relationship between diabetes and COVID-19 disease is ACE-2 [10,12]. It is generally accepted that ACE-2 is the main receptor for the entrance of the SARS-CoV-2 virus. Although the ACE enzyme is in high concentrations in the lung vasculature, it is also found in other tissues and cells throughout the organism. One of these other places are the beta cells of the pancreatic islets of Langerhans. It was seen that SARS-CoV-2 virions infect, damage, and destroy directly the beta cells of the pancreas, thus reducing the body's capacity to secrete insulin and regulate blood glucose [12]. This argument is further supported by the fact that COVID-19 infection can produce hyperglycemia in nondiabetic patients, suggesting a possible injury to pancreatic beta cells [12].

In summary, be it by direct hyperglycemic, increased severity of COVID-19, inflammation and insulin resistance, diabetic comorbid complications, or ACE-2 mediated entrance and lysis of pancreatic beta cells, diabetes undoubtedly increases COVID-19 severity.

Use of Insulin

A retrospective observational study in US hospitals during the initial part of the COVID-19 pandemic had shown that the mortality rate was 28.8% higher in patients with DM. A similar effect was detected in patients having significant hyperglycemia compared to patients with no hyperglycemia [13]. The prevalence of a more severe outcome by SARS-CoV-2 infection was also higher in patients of the male gender, and the risk of hospitalization was greater in patients with a BMI ≥ 30 kg/m^2. There was an even greater risk of a dead outcome in patients with obesity and other comorbidities [14]. The increased mortality rates were attributed to a greater occurrence of ARDS, septic shock, acute renal injury, and DIC, after adjustment of demographics and disease severity [15]. In Diabetic patients, the presence of microvascular and macrovascular complications, chronic renal insufficiency, and use of insulin were found to be independent risk factors for increased mortality [16,17].

Hyperglycemia affects pulmonary function and has an inductive effect on influenza viral replication [18]. Additionally, animal models have demonstrated the association of diabetes with lung structural changes, increased permeability of the alveolo-capillary membrane, and collapsed of alveoli [19]. There has been an increased frequency of presentation with Diabetic Ketoacidosis and extreme insulin resistance in patients presenting with COVID-19 [20]. Patients with COVID-19 infection had a range between 7-17 days in the ICU. These patients expressed lower levels of muscle glucose transporter type 4 (GLUT-4), insulin-dependent glucose transporter, and beta-serine/threonine protein kinase (AKT2), leading to insulin resistance [21]. Prolonged bed rest was also associated with insulin resistance [22]. A reduction of mitochondrial function and oxidative phosphorylation in bed rest studies were also thought to contribute to insulin resistance [23]. The clinical syndrome is further complicated using catecholamines and corticosteroids for the treatment of COVID-19 complications [24,25]. Historically, infection with viral pathogens, rotavirus, mumps, rubella, and other enteroviruses was found a common trigger for the onset of type 1 diabetes mellitus in susceptible patients [26,27]. This mechanism of molecular mimicry has been speculated to be one of the causes of hyperglycemia in COVID-19 patients [28]. Insulin therapy remains the most used therapy for hyperglycemia in COVID-19 pandemic, although, in the pre-pandemic era, multiple trials have shown the efficacy and safety of DPP IV in ICU patients [29]. Insulin plays a major role in modulating the immune response by controlling the effects of monocytes/macrophages, neutrophils, and T cells. Insulin therapy is thought to improve outcomes by protecting the endothelium, perhaps by inhibiting high levels of NO [30]. Proactive treatment with ultra-long-acting basal insulin dosage and correctional boluses should be encouraged to reduce the risk of deterioration of the altered metabolic state including episodes of hypoglycemia in patients with type 1 and type 2 diabetes. Patients who are already in ongoing treatment with insulin, should have an accurate control with different combinations of insulin to diminish even more the risk of metabolic alterations [15,31].

Other glucose lowering medications have also been under discussion for the treatment of diabetic patients with COVID-19 infections. In fact, studies show that these medications, such as GLP-1, RA, and SGLT-2 inhibitors, could have beneficial effects in distal organs including the cardiovascular and renal system. In Croatia, a study was conducted in patients with a high BMI (> 30 kg/m^2) [14]. These patients could be treated with glucagon-like peptide-1 receptor agonists that were only used previously in patients with BMI > 35 kg/m^2, and in patients

with cardiovascular disease and type 2 diabetes, GLP-1 RA could be given with lower BMI levels such as > 28 kg/m^2 for a greater cardiovascular protection [14]. Another medication that has shown little side effects in patients with an ongoing infection is DPP IV [15,30]. Metformin could be used, checking renal and liver function prior to administration. Like insulin, metformin could also have an anti-inflammatory effect [23]. Patients who are taking other oral antihyperglycemic medications besides the ones mentioned above, should stop administration during the period of acute illness, since they have shown to increase the risk of major side effects [32].

Fluctuating insulin resistance, dynamic glycemic monitoring, and management, and safety of health care workers in the process have been the major challenges in the management of COVID-19 patients in ICU [33-36]. Nurses from all over the world were redirected to work in critical care units with higher demands, where previous training was a must [37]. Intravenous insulin has been predominantly used in ICU due to its rapid mode of onset and easy titration, however, there is a considerable risk of hypoglycemic episodes with the use of intravenous insulin. While practicing bundled therapy ideas by WHO [33], repeated blood glucose monitoring and titration are particularly challenging [38,39]. Studies show that serum glucose levels should be checked every one or two hours until an adequate infusion rate has been reached, afterwards levels can be checked every four hours [23].

Currently, glycemic management in COVID-19 patients includes bedside Blood Glucose (BG) levels (100 to 180 mg/dL for noncritically ill patients and 140 to 180 mg/dL in critically ill patients) with structured insulin treatment protocols [29]. These patients require point-of--of-care blood glucose (POC BG) checks before meal and bedtime for patients who are eating and every 4-6 hours [29]. Food and Drug Administration (FDA) approved continuous glucose monitoring (CGM, Freestyle Libre (Abbott), and Dexcom G6) and home glucose (restricted to use for only one patient) devices for hospital use during the COVID-19 pandemic [40]. These devices are used in place of Point-Of-Care Blood Glucose (POC BG) checks to minimize the frequency and duration spent in hypoglycemia, Personal Protective Equipment (PPE) use, and contact time of healthcare workers with the patient [41]. Continuous subcutaneous insulin infusion (CSII/pump) and continuous glucose monitoring have shown to have a positive impact in diabetic patients under daily treatment. Healthcare workers should be advised if the patient is using a CSII on arrival at the hospital, and the decision to continue or not the administration of the drug should be made [42]. Continuous glucose monitoring has been deemed a reasonable solution to the hypoglycemia issue, for which the FDA has given the enforcement discretion to the hospital for CGM use in ICU and inpatient stay [43]. Different studies have demonstrated the efficacy of CGM in reducing the incidence of hypoglycemia in diabetic patients on insulin, despite the negative impact of dehydration, edema, and dehydration on the accuracy of reading [44,45]. FDA has recently approved the use of a home glucometer in inpatient services by the patient, to minimize the interruption in glucose monitoring and keeping healthcare workers safe [46]. Although the Dexcom sensors can be read at a distance of 20 feet, freestyle libre sensors need to keep the reader in the immediate vicinity of the sensor to read the results. Possibly patients can be taught how to use the reader in noncritical situations to lessen the burden on the healthcare workers [6]. It is important to remember that these devices require previous training, and that appropriate interdisciplinary staff should participate in the patients care [32]. Switching to telehealth consults in this pandemic era should be highly considered in patients that require a stricter control of their health, while limiting exposure to hospital environments [30].

Insulin in Critical Patients with COVID-19

There exists a bidirectional correlation between hyperglycemia and inflammation [22]. Hyperglycemia is caused by the inflammatory state of COVID-19 infection, amplified especially in preexisting diabetes and obesity, leading to worsening of prognosis in COVID-19 patients [22,47,48].

In 2013, Dandona, et al. conducted a crossover controlled study in type 1 diabetes patients by infusing either of insulin (2 U/L) with 5% dextrose (100 mL/h)/5% dextrose (100 mL/h)/physiological saline (100 mL/h) for 4 hours on 3 days separated by 1 week showing (1) Free fatty acids (FFA) decreased with insulin and increased especially with dextrose compared to saline infusion (2) High-Mobility Group-B1 (HMGB-1), Reactive Oxygen Species (ROS) generation by polymorphonuclear neutrophils (PMN) decreased with insulin infusion, increased with dextrose and remains unchanged with saline infusion (3) There is also decrease in C-reactive protein (CRP) and rapid upon activation T expressed and secreted (RANTES, CCL-5) with insulin infusion while these parameters remains unchanged with dextrose/saline infusion (4) p47phox expression (subunit of NADPH oxidase in mononuclear cells) is suppressed with insulin infusion while it remains unchanged with dextrose/saline infusion (5) TLR-1, TLR-2, TLR-4, and CD14 expression in mononuclear cells (MNC) increased with insulinwhile TLR-1, TLR-2, TLR-4 decrease and CD14 remains unchanged with dextrose infusion. There is no change in these parameters following saline infusion (6) TLR-4 protein level in MNC increases with dextrose and remains unchanged with insulin/saline infusion (7) HMGB-1 protein and p38 Mitogen-Activated Protein (MAP) kinase in MNC decrease with insulin, these parameters in addition with c-Jun NH2-terminal kinase (JNK)-1 decrease with dextrose, and remains unchanged with saline infusion (8) Platelet cell adhesion molecule

expression decrease with insulin infusion and remains unchanged with dextrose/saline infusion [46]. Thus, the authors concluded anti-inflammatory effects of insulin in comparison with the inflammatory effects of glucose in these patients [2]. Therefore, insulin therapy should be used in the management of hyperglycemia in COVID-19 patients due to its anti-inflammatory, anti-prothrombotic, and fibrinolytic properties [49].

In 2005, Vanhorebeek, et al. conducted a prospective randomized controlled study to determine the beneficial effects of insulin therapy in critically ill patients demonstrating (1) Glycemic control of insulin therapy resulted in the protection of mitochondrial compartment and innate immunity (2) Decrease in morbidity and mortality (3) Non-glycemic effects included improvement in serum lipid profile, preventing catabolic state due to critical illness and myocardial protection concluding better overcome of critical illness on treatment with insulin therapy [50].

Insulin Therapy in Steroid-Induced Hyperglycemia

Publication of RECOVERY Trials elicited the mortality benefit of Dexamethasone in COVID-19 infected patients [51]. REACT working group trial further strengthened the findings [52], however, another randomized clinical trial conducted in Brazil showed no difference in 28 days mortality, but patients on steroids required increased insulin dosage [53]. Treatment with steroids leads to steroid-induced diabetes, the severity of which varies based upon the duration and dose of steroid use, eGFR, age, and severity of illness [54-57]. Acute Hyperglycemia has been reported in COVID infected patients with no reported diabetes status [58-60], and a positive correlation was found between admission hyperglycemia and disease severity and mortality [61,62]. This effect is hypothesized to be partially ACTH-dependent stress response to inflammatory mediators like TNFα and IL-1 due to the release of CRH [63]. Hypercortisolism leads to an increased rate of hepatic gluconeogenesis and inhibits glucose utilization in organs causing insulin resistance [64]. Acute hyperglycemia has been shown to support SARS-CoV-2 replication via the up-gradation of hypoxia-inducible factor 1α (HIF1α), which in turn further supplements the glycolytic pathway and IL-1β expression [65]. Therefore, the patient who is already diabetic at the time of infection has more disease manifestations. Stress, hyperglycemia, insulin resistance, and counterregulatory mechanisms due to ongoing inflammation lead to loss of muscle mass, which in turn translates to detrimental clinical outcomes [66]. Administration of glucocorticoids in an ongoing catabolic state, in the presence of catecholamines, will further accentuate hyperglycemia [67-69]. The immunosuppressive effect of corticosteroids delays the viral clearance from the host's body [70]. Tight glycemic control in ICU patients reduced mortality in cardiac surgery patients from 8% to 4.6% where only 13% of the patients were diabetic. The major benefit was seen in patients having sepsis and polyorgan failure [71]. The protective effect was attributed to protection against the development of organ failure [72]. Two randomized control trials failed to show any mortality benefit in 28 or 90 days, however, those trials were terminated earlier due to patient safety concerns and frequency of hypoglycemia in critical patients [73,74]. Glucose infusion along with exogenous insulin has been shown to inhibit lipolysis, increase peripheral tissue glucose uptake, and decrease the concentration of inflammatory markers, but failed to inhibit hepatic endogenous stress-induced glycogenolysis [75,76]. Although conventional insulin supplementation with glucose has shown an equivocal effect on protein turnover [77,78], hyper insulin supplementation reaching a level of 1500 pmol/L has been shown to suppress the catabolic state-induced protein degradation [75]. Retrospective studies involving the use of exogenous insulin are an appealing topic for future research, but the definite impact of insulin supplementation in COVID-19 patients cannot be predicted [79].

Side Effects and Contraindications

One of insulin's most important side effects is hypoglycemia. This is true whether insulin is being used for the adequate glycemic control of diabetic patients, hyperglycemia related to COVID-19, or glucocorticoid use [29,80]. Hypoglycemia is especially frequent in intensive care settings. It can be worse in the case of hospitalized severely ill COVID-19 patients because of a grave insulin resistance that is commonly seen in this disease [81]. With the resolution of COVID-19, this inflammation quickly subsides, and the secondary insulin resistance goes down as well, rapidly decreasing the need for insulin and increasing the risk of hypoglycemia. Therefore, it is important to reduce the insulin dose as patients begin to recover from the disease to diminish the risk of future hypoglycemia. Yu, et al. [7] developed a retrospective study where they discovered that 40.6% of patients who died while on insulin treatment experienced hypoglycemia during their hospital stay. In contrast, all patients who did not take insulin survived and only 1.4% of them suffered hypoglycemia.

Apart from hypoglycemia, another important side effect of insulin is hypokalemia. This is mainly because insulin is one of the three main hormones that promote potassium influx into the cell from plasma [73]. Potassium balance is even more crucial in COVID-19 patients as it is a common electrolyte disturbance associated with the disease course [20,74]. This is due to several possible mechanisms. Gaetano, et al. found out in a retrospective analysis that two important risk factors for hypokalemia among COVID-19 patients were female sex and diuretic use [20]. Moreover, it is believed that the interaction between SARS-CoV-2 and

the renin-angiotensin-aldosterone system originates a secondary hyperaldosteronism induced by the increased concentrations of angiotensin 2 found in COVID-19 infected patients. This latter mechanism may be due to the disruption of ACE-2 by the binding of SARS-CoV-2 [20].

After a thorough search through the current up-to-date bibliography, we found no specific contraindications for insulin use in the setting of COVID-19. As stated before, both hypoglycemia and hypokalemia are common in the setting of hospitalized, moderately to severely ill COVID-19 patients. Because both hypoglycemia and hypokalemia are important insulin side effects, extreme caution is advised when treating COVID-19 patients with insulin and accompanying hypoglycemia or hypokalemia.

Although not a specific contraindication by itself, it is relevant to state that recent studies tend to show that insulin increases mortality in COVID-19 patients with comorbid diabetes [7,80]. Yang, et al. analyzed 18 articles involving a totality of 12,277 patients in their systematic review [80]. They concluded that there was an overall increase in the risk of mortality, severe and/or critical COVID-19 complications, and, finally, in-hospital admissions. The exact mechanisms to explain this occurrence are unknown, however, some are hypothesized. One of them is that insulin may promote the release of proinflammatory cytokines from macrophages in the setting of sepsis [82-85]. Furthermore, insulin may induce lung inflammation during sepsis [86-90]. An analysis to determine the underlying cause of injury mediated by insulin was conducted in patients without an episode of hypoglycemia during their hospital stay [91]. Studies demonstrated that SARS-CoV-2 and insulin activated the NLRP3 inflammasome in macrophages [92]. This activation stimulates pro-IL-1β maturation leading to a pro-inflammatory response. Diabetic patients are also suffering from increased glucose concentration and free fatty acids that also contribute to IL-1β formation and activation of an immune response. This ongoing inflammatory state could lead to a greater risk of SARS-CoV-2 infection. High glucose levels favored the replication of the virus inside monocytes [65].

Furthermore, there remains a risk of a worse COVID-19 prognosis increase with poorer metabolic control [87]. For example, it was revealed that insulin requirements paralleled the severity of COVID-19 infection in critically ill patients [88]. This demonstrates a possible link between insulin requirements and a poorer prognosis of the disease. This point is further explained by Kow, et al. who argue that the association between insulin use, and mortality is subject to differences in glycemic control between insulin and non-insulin users [89].

It is still unclear whether insulin or other predisposing factors are held accountable for the high level of mortality observed in patients with COVID-19 and type 2 diabetes. This still presents a great challenge for physicians that are faced everyday with this ongoing pandemic. Insulin is usually preferred over other antidiabetic drugs for the control of glycemia in in-patient settings as insulin can be used for mild, moderate, and severe SARS-CoV-2 infection [90]. In synthesis, regarding contraindications, insulin use in diabetic patients should not be stopped due to COVID-19 infection as there is not enough evidence to suggest that its sole use is detrimental. Further randomized controlled trials are needed to confirm these results.

Conclusion

Present research studies are conveying mounting evidence of morbidity and mortality of COVID-19 patients with DM. But the results remain unclear and controversial, therefore, we conducted this review study for a clearer picture. DM is causing more hospital admissions for COVID-19 patients than in nondiabetic patients, and more severe complications are prominent due to the amalgamation of COVID-19 with DM. Insulin treatment is reported to relate to higher mortality rates and other adversative consequences in patients with COVID-19 and DM, however, the reports are not conclusive. Insulin is still the favored therapy for hyperglycemia in hospitalized patients who have moderate to acute COVID-19. It is mandatory to always use insulin for patients with type 1 DM to prevent ketoacidosis, while the use of insulin therapy might be temporary for type 2 DM patients [93,94]. Additional effects of COVID-19 infection on the use of insulin and potential management and treatment options are still being investigated by researchers all around the world. We recommend patients with DM should be more carefully treated according to the currently available guidelines to prevent any unwanted complications and mortality.

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Conflict of Interest

The authors declare no conflict of interest.

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