The Optimal Medical Therapy for Glycemic Control in COVID-19

Hidekatsu Yanai

Abstract

Diabetes is highly linked to the severity of coronavirus disease 2019 (COVID-19). My recent meta-analysis also suggested a higher prevalence of diabetes in severe COVID-19 as compared with non-severe COVID-19. Recent observational studies have shown that hyperglycemia was significantly associated with severity of COVID-19 in both diabetic and non-diabetic patients. To prevent worse outcome of COVID-19, more tight glucose control is required. I studied the association between hyperglycemia and worse outcome of COVID-19, the putative beneficial and harmful effects, and clinical outcomes of oral hypoglycemic drugs and insulin use in glycemic control among COVID-19 patients, by searching literatures. Although there were some negative studies, the meta-analysis reported that the treatment using metformin was associated with reduction in mortality due to COVID-19. One study showed that treatment with sitagliptin, one of dipeptidyl peptidase-4 (DPP4) inhibitors, during hospitalization was associated with reduction of mortality, with a clinical improvement as compared with patients on the standard care. There were no clinical studies showed effects of glucagon-like peptide-1 receptor agonists, pioglitazone and sulfonylurea on COVID-19 outcomes. Regarding sodium-glucose cotransporter 2 (SGLT2) inhibitors, a case of euglycemic diabetic ketoacidosis (DKA) associated with COVID-19 and a case of DKA that was difficult to distinguish from COVID-19 were reported. COVID-19 patients who need hospital care may deteriorate rapidly, an early and appropriate initiation of insulin therapy in hyperglycemic COVID-19 patients may be to be encouraged.

Keywords: Glucose control; COVID-19; Oral hypoglycemic drugs; Insulin therapy

Introduction

Coronavirus disease 2019 (COVID-19) induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has reached a pandemic level. Diabetes is one of the most important comorbidities linked to the severity of COVID-19. My meta-analysis of 13 studies showed that the existence of diabetes was significantly associated with severity of COVID-19 [1]. A recent study involving COVID-19 patients admitted to the intensive care unit (ICU) (n = 495) showed that hyperglycemia was significantly associated with prolonged ICU stay, mechanical ventilation use, and higher mortality [2]. Tighter blood glycemic control is warranted to COVID-19 patients.

Here, I will show the association between hyperglycemia and worse outcome of COVID-19, the putative beneficial and harmful effects, and clinical outcomes of oral hypoglycemic drugs and insulin use in glycemic control among COVID-19 patients, by searching literatures.

Hyperglycemia and Worse Outcome of COVID-19

The activation of the hypothalamic-pituitary-adrenal axis by severe infection induces over-secretion of insulin-counteracting hormones such as cortisol, growth hormone and glucagon, which increases plasma glucose. Furthermore, inflammatory cytokines induce insulin resistance [3]. A multi-center retrospective study showed that mortality and mechanical ventilation use were significantly more frequent in the hyperglycemic group (average blood glucose (BG) > and = 140 mg/dL) than the normoglycemic group (average BG < 140 mg/dL) (31.4 % vs. 16.6%; 50.0% vs. 37.2%, respectively) [2]. Hyperglycemia (hazard ratio (HR), 1.79; 95% confidence interval (CI), 1.14 - 2.82) predicted the in-hospital mortality. Steroids use (odds ratio (OR), 1.521; 95% CI, 1.054 - 2.194) and triglycerides > 150 mg/dL (OR, 1.62; 95% CI, 1.109 - 2.379) on admission were associated with hyperglycemia [2]. Yang et al studied the association between fasting plasma glucose (FPG) and 28-day mortality in COVID-19 patients [4]. Higher levels of neutrophil counts and D-dimer, and lower levels of lymphocyte counts and albumin, and higher incidence of fatal complications were observed in patients with diabetes. FPG with 7.0 - 11.0 (HR, 1.90; 95% CI, 1.11 - 3.25) and ≥ 11.1 mmol/L (HR, 2.09; 95% CI, 1.21 - 3.64) were independent predictors of 28-day mortality [4]. A pooled analysis on the association between hyperglycemia and outcomes of COVID-19 showed that hyperglycemia was significantly associated with higher incidence of critical illness (OR, 1.837; 95% CI, 1.368 - 2.465)
Glycemic Control in COVID-19

Table 1. Putative Beneficial and Harmful Effects, and Clinical Outcomes of Metformin Use in Glycemic Control Among COVID-19 Patients

<table>
<thead>
<tr>
<th>Putative beneficial effects</th>
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<td>Metformin improves insulin resistance which is induced by increased inflammatory cytokines.</td>
<td>Development of lactic acidosis in hypoxic situation.</td>
<td>In a case-control study, the incidence of life-threatening complications was significantly higher in the metformin group than the non-metformin group (28.6% vs. 7.4%, P = 0.004) [9].</td>
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<td>Reduced production of proinflammatory cytokines, and alleviation of lung injuries in animals. Direct inhibition of SARS-CoV-2 infection [7].</td>
<td></td>
<td>Metformin was significantly associated with a higher incidence of acidosis, especially in severe COVID-19 patients, however, not with 28-day mortality [10].</td>
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<td>Suppresion of IL-1β-induced secretion of IL-6 in macrophages, vascular smooth muscle and endothelial cells [8].</td>
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As a putative harmful effect, development of lactic acidosis in hypoxic situation such as acute respiratory distress syndrome (ARDS) and severe pneumonia should be considered.

In a case-control study conducted by Gao et al, the incidence of life-threatening complications was significantly higher in the metformin group than the non-metformin group (28.6% vs. 7.4%, P = 0.004) [9]. In a retrospective study (n = 1,213), the treatment using metformin was significantly associated with the development of acidosis, especially in individuals with severe COVID-19, however, not with 28-day mortality [10]. A health record data analysis of 25,326 subjects showed that metformin was independently associated with a significant reduction in mortality among COVID-19 individuals with diabetes (OR, 0.33; 95% CI, 0.13 - 0.84; P = 0.0210) [11]. Further, metformin use was associated with reduced mortality in women by propensity matching (OR, 0.759; 95% CI, 0.601 - 0.960) [12]. The in-hospital mortality was significantly lower in the metformin group (2.9%) than in the non-metformin group (12.3%) [13]. The meta-analysis (5 studies, n = 6,937) elucidated that metformin was associated with reduction in mortality (RR, 0.54; 95% CI 0.32 - 0.90, P = 0.02) [14].

Putative Beneficial and Harmful Effects, and Clinical Outcomes of Oral Hypoglycemic Drugs Use in Glycemic Control Among COVID-19 Patients

**Metformin**

Metformin, a drug for the treatment of type 2 diabetes, reduces the proinflammatory cytokines production (Table 1 [7-14]). Alleviation of lung injuries by metformin was observed in animals and a direct inhibition of SARS-CoV-2 infection by metformin has been supposed [7].

Metformin was reported to inhibit interleukin-6 (IL-6) release in mucosal cells, macrophages, vascular smooth muscle and endothelial cells [8]. For glycemic control, metformin improves insulin resistance which is induced by increased inflammatory cytokines.

One case-control study showed a significant association between metformin and critical complications. Another observational study reported an association of metformin with the development of acidosis in severe COVID-19, but not with mortality. Other three studies showed that metformin use was associated with a significant reduction in mortality in COV-
ID-19, and the meta-analysis also showed that metformin was associated with decrease of mortality.

**Incretin-related drugs**

Dipeptidyl peptidase-4 (DPP4) inhibitors increase secretion of insulin, anabolic hormone, which may be beneficial for the treatment of severe infection. The identified DPP4 networks are highly enriched in viral processes required for viral entry and infection, therefore, DPP4 was proposed as an important putative target for the treatment of COVID-19 [15]. A meta-analysis reported a significant reduced CRP levels by DPP4 inhibitors as compared with placebo [2]. Sitagliptin was reported to improve inflammatory status by affecting on NF-kappa-B signaling [16]. The S1 domain of SARS-CoV-2 spike glycoprotein potentially interacts with DPP4 [17]. DPP4 inhibitors can be the therapeutic candidate for COVID-19 by blocking the entry of SARS-CoV-2 into human body [18]. In type 2 diabetic patients, liraglutide (GLP-1 RA) significantly reduced serum CRP levels [2].

**Table 2. Putative Beneficial and Harmful Effects, and Clinical Outcomes of Incretin-Related Drugs Use in Glycemic Control Among COVID-19 Patients**

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<td>DPP4 inhibitors are unlikely to develop hypoglycemia.</td>
<td>No applicable data</td>
<td>Sitagliptin use during hospitalization was associated with reduced mortality (HR, 0.44; 95% CI, 0.29 - 0.66; P = 0.0001), with clinical improvement (60% vs. 38%; P = 0.0001) and with more hospital discharges (120 vs. 89; P = 0.0008) as compared with the standard care [19].</td>
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**Pioglitazone**

IL-6 expression was reduced by pioglitazone in monocytes, white adipose tissue and cardiomyocytes (Table 3 [2, 21-24]). Pioglitazone significantly reduced serum CRP levels. A previous meta-analysis reported that pioglitazone significantly reduced high-sensitivity CRP levels in type 2 diabetic patients [2]. Progressive atherosclerosis may be associated with the development of COVID-19. Oxidized LDL (ox-LDL) plays a crucial role in atherogenesis. Uptake of ox-LDL by macrophages activates the reprogramming of innate immunity, which is termed “trained immunity.” Ox-LDL-trained macrophages may induce over-secretion of cytokines triggered by...
Progressive atherosclerosis is associated with the development of severe COVID-19. Oxidized LDL (Ox-LDL) plays an important role for atherogenesis. Uptake of Ox-LDL by macrophages activates the reprogramming of innate immunity, “trained immunity.” Ox-LDL-trained macrophages infected with SARS-CoV-2 increase cytokine release, which leads to lung injury. Inhibition of macrophage training by pioglitazone may suppress the cytokine storm induced by SARS-CoV-2 infection [21].

### Table 3. Putative Beneficial and Harmful Effects, and Clinical Outcomes of Pioglitazone and Sulfonylurea in Glycemic Control Among COVID-19 Patients

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<td>IL-6 expression was suppressed by pioglitazone in monocytes, white adipose tissue and cardiomyocytes. Pioglitazone significantly reduced serum CRP levels. A meta-analysis demonstrated that pioglitazone significantly lowered serum hs-CRP levels in type 2 diabetic patients [2].</td>
<td>As my opinion, pioglitazone may possibly exacerbate pulmonary congestion or acute respiratory distress syndrome (ARDS) which need critical management of body fluid by increasing fluid retention.</td>
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<td>Sulfonylurea increases secretion of insulin, anabolic hormone, which may be beneficial for the treatment of severe infection.</td>
<td>Sulfonylurea is likely to develop hypoglycemia.</td>
<td>A combination therapy of metformin and sulfonylureas was most commonly associated with the development of hypoglycemia (65.75%) [24].</td>
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<td>Channel activity was found for the envelope protein of coronaviruses, and the ion channel was inhibited by gliclazide [22].</td>
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SARS-CoV-2 infection in the lung. Therefore, the pioglitazone-mediated inhibition of macrophage training could reduce the cytokines-induced lung injuries [21].

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### Sulfonylurea

Sulfonylurea increases secretion of insulin, anabolic hormone, which may be beneficial for the treatment of severe infection (Table 3 [2, 21-24]). However, sulfonylurea is likely to develop hypoglycemia. Channel activity was found for the envelope protein of coronaviruses, and the ion channel was inhibited by gliclazide [22]. Essential for viral replication, the main protease has been explored as a promising target for the drug discovery process. The virtual screening pipeline relies on the known 3D properties of noncovalent ligands and features of crystalized complexes, applying consensus analyses in each step. Glibenclamide presented 3D similarity to known ligands, reasonable predicted binding modes and micromolar predicted binding affinity values. Glibenclamide was identified as promising inhibitor of the main viral protease [23].

Shah et al analyzed the data retrospectively from 146 patients of type 2 diabetes reporting to the emergency department during lockdown period with symptoms suggestive of hypoglycemia [24]. A combination of metformin and sulfonylureas was most commonly associated with the development of hypoglycemia (65.75%) in patients with type 2 diabetes during the COVID-19 lockdown [24].

### Sodium-glucose cotransporter 2 (SGLT2) inhibitors

Owing to their pharmacological characteristics, SGLT2 inhibitors might cause adverse effects in patients with COVID-19.
and so cannot be recommended [25]. People with diabetes should be encouraged to continue medication prescribed for hypertension, diabetes or dyslipidemia. Furthermore, patients with diabetes and COVID-19 infection should follow their usual antidiabetic treatment with the exception of SGLT2 inhibitors [26]. Avoidance of diabetic ketoacidosis associated with SGLT2 inhibitors is of particular medical importance during the COVID-19 pandemic [27].

A 52-year-old male with type 2 diabetes on empagliflozin and no history of diabetic ketoacidosis (DKA) presented with symptoms of COVID-19 as well as laboratory findings consistent with euglycemic DKA. SGLT2 inhibitors should be held as early as possible in COVID-19 patients due to the risk of euglycemic DKA [28]. The patient of euglycemic DKA due to empagliflozin use was initially suspected to be a case of COVID-19 [29]. During the pandemic of COVID-19, euglycemic DKA due to SGLT2 inhibitors may disrupt emergency medical care.

Insulin Therapy in Glycemic Control Among COVID-19 Patients

Hyperglycemia was significantly associated with severity of COVID-19 in both diabetic and non-diabetic patients. To prevent worse outcome of COVID-19, more tight glucose control is required. To obtain prompt and tight glycemic control, insulin therapy may be useful.

In the retrospective study investigating 689 patients with COVID-19 and type 2 diabetes, insulin therapy was associated with a significant increase in mortality (adjusted HR, 5.38; 95% CI, 2.75 - 10.54) [30]. Insulin therapy was associated with enhanced systemic inflammation and aggravated injuries of vital organs. We should not conclude that insulin treatment is harmful for glycemic control in COVID-19 by this result. The need for insulin may reflect the severity of COVID-19 and the duration of diabetes.

Agarwal et al studied pre-existing risk factors for mortality in hospitalized COVID-19 patients with diabetes [31]. Insulin therapy that reflects the duration of diabetes was predictive of mortality [31].

In the analysis of 562 ICU patients, the time in range (TIR) (70 - 150 mg/dL) and the daily insulin dose in critical COVID-19 patients and non-COVID-19 patients were investigated [32]. The TIR in COVID-19 patients (44.4%) was significantly lower than non-COVID-19 patients (68.5%). COVID-19 patients needed more daily insulin dose (8.37 units) than non-COVID-19 patients (6.17 units). A lower TIR was associated with ventilator use, and a higher TIR was associated with lower mortality, suggesting a significant association between poor glycemic control and poor COVID-19 outcomes among ICU patients.

Wu et al analyzed characteristics, insulin therapy and inflammatory markers of diabetic patients admitted to ICU with COVID-19 [33]. During highly inflammatory state, extremely high insulin doses (2.2 units/kg/day) were required for glycemic control. With reduced inflammation, daily insulin requirement decreased and glycemic control improved.

COVID-19 patients who need hospitalization seemed to deteriorate rapidly; therefore, an early initiation of an appropriate insulin therapy in hyperglycemic patients with COVID-19 is to be encouraged [34]. Considering various studies, the target glucose range in COVID-19 patients may be 140 - 180 mg/dL [35]. Beyond the control of hyperglycemia, an early initiation of insulin therapy is considered to have beneficial effects for immunomodulation, regulate the renin-angiotensin system (RAS) which can induce acute lung injury [36].

During highly inflammatory status due to COVID-19, the achievement of an appropriate glycemic control is difficult and needs high doses of insulin. To reduce deaths and severe cases due to COVID-19, it is important to obtain good glycemic control even with a large amount of insulin from an earlier stage.

Table 4. Putative Beneficial and Harmful Effects, and Clinical Outcomes of SGLT2 Inhibitors in Glycemic Control Among COVID-19 Patients

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Conclusions

Although there were two negative studies, the meta-analysis showed that metformin use was associated with reduction in mortality of COVID-19 patients. One study showed that sitagliptin was associated with reduction of mortality and clinical improvement compared with the standard care. There were no clinical studies showed effects of GLP-1 RAs, pioglitazone and sulfonylurea on COVID-19 clinical outcomes. Regarding SGLT2 inhibitors, a case of euglycemic DKA associated with COVID-19 and a case of DKA that was difficult to distinguish from COVID-19 were reported. COVID-19 patients who need hospitalization seemed to deteriorate rapidly, therefore, an early initiation of an appropriate insulin therapy in hyperglycemic patients with COVID-19 is to be encouraged.

Acknowledgments

Not applicable.

Financial Disclosure

Author has no financial disclosure to report.

Conflict of Interest

The author declares that he has no conflict of interest concerning this article.

Informed Consent

Not applicable.

Author Contributions

H.Y. designed the research, and collected and analyzed data. H.Y. wrote and approved the final paper.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

References

16. Mozafari N, Azadi S, Mehdi-Alamdarlou S, Ashrafi H, Azadi A. Inflammation: A bridge between diabetes and
22. Singh Tomar PP, Arkin IT. SARS-CoV-2 E protein is a potential ion channel that can be inhibited by Gliclazide and Memantine. Biochem Biophys Res Commun. 2020;530(1):10-14.