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Glycemic control using intermittently scanned continuous glucose monitoring in patients with diabetes requiring methylprednisolone therapy for severe COVID-19

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Abstract: In patients with severe coronavirus disease 2019 (COVID-19) with diabetes, glycemic control is essential for a better outcome, however, we face difficulty controlling hyperglycemia induced by high-dose glucocorticoids. We report five cases of severe COVID-19 patients with diabetes, whose glycemic control was managed using an intermittently scanned continuous glucose monitoring (isCGM) system during methylprednisolone therapy. Patients using isCGM showed significantly lower average blood glucose levels and significantly higher total daily insulin dose during the methylprednisolone therapy, compared to patients under regular blood glucose monitoring. The use of isCGM enables remote glucose monitoring, and this can reduce the risks of healthcare workers who have frequent contact with the patients. Thus, we suggest that using isCGM should be considered in hospitalized patients with diabetes under the COVID-19 pandemic to achieve better glycemic control and to minimize the possible risks of healthcare workers.

***Keywords*:** COVID-19, hyperglycemia, isCGM

Introduction

For patients with diabetes who are infected by the coronavirus disease 2019 (COVID-19), recent data have shown the importance of good glycemic control for better outcomes (*1*). Methylprednisolone therapy is effective in reducing mortality for patients with severe COVID-19 (*2*). However, in patients who are comorbid with COVID-19 and diabetes, hyperglycemia induced by methylprednisolone therapy is often difficult to control, and there is no well-established insulin regimen to manage this hyperglycemia.

To adjust the appropriate insulin dosage for controlling blood glucose levels that fluctuate with diet and glucocorticoid treatment, timely monitoring by point-of-care (POC) blood glucose testing is recommended (*3*). However, during a pandemic with limited medical resources, performing frequent blood glucose testing is a challenging task because it can increase the risk of infection for the medical staff, and there is a need for sufficient personal protective equipment (PPE) to manage the task.

Previous studies have shown that in hospitalized patients with severe COVID-19, the use of continuous glucose monitoring in combination with POC testing significantly reduced the frequency of POC testing (*4,5*). Intermittently scanned CGM (isCGM; FreeStyle Libre Flash glucose monitoring system, Abbott Laboratories, Chicago, IL) is an easy handling device, and the glycemic data can be remotely monitored by healthcare professionals when a patient scans the sensor with his/her smartphone. The use of isCGM for inpatient glycemic control is still not widespread in Japan due to insurance coverage matters (Supplementary document 1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*).

However, considering the COVID-19 pandemic, isCGM is effective for obtaining better glycemic control and can be a safe device for healthcare workers to minimize the frequency of patient contact. Therefore,

isCGM was used in some patients who were capable of scanning their sensor with their smartphone, which enabled healthcare professionals to remotely and continuously monitor patients' glycemic data. Thus, utilizing isCGM to assess trends in blood glucose levels allows timely and adequate adjustment of the insulin dose.

In our hospital, patients with severe COVID-19 were treated with methylprednisolone from the early stages of infection according to the dosing regimen used for acute respiratory distress syndrome and severe pneumonia (*6*). Glycemic control under COVID-19 infection and steroid use has been a major issue in patient management. Therefore, this observation aimed to examine the efficacy and safety of isCGM in controlling hyperglycemia induced by methylprednisolone therapy in patients with diabetes who were infected with severe COVID-19.

Patient characteristics

We studied adult patients with diabetes and severe COVID-19 who required methylprednisolone therapy and were hospitalized at CHNCGM between April 1 and August 18, 2021 (Supplementary document 2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*). Intermittently scanned CGM (isCGM) was used in 5 patients, and the rest of the 21 patients were controlled by regular blood glucose monitoring (BGM). Since isCGM requires self-scanning of glucose data, intubated patients and/or older patients who have difficulties managing the device were excluded. Therefore, intubated patients and patients aged over 65 was excluded from analysis, leaving 14 patients controlled by BGM. Patient characteristics on admission are shown in Supplementary Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*).

There were no significant differences in age, sex, body mass index (BMI), systolic blood pressure, body temperature, oxygen saturation, and comorbidities between the two groups. According to the laboratory data, there were no significant differences in the levels of plasma glucose, HbA1c, serum albumin, aminotransferase, alanine aminotransferase, lactate dehydrogenase, serum creatinine, C-reactive protein, D-dimer, and neutrophil count. The lymphocyte count was significantly higher in the isCGM group than in the BGM group.

The severity of COVID-19 infection, treatment regimen, and outcomes are shown in Supplementary Table S2 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*). Regarding COVID-19 severity, critical cases were two (40.0%) and nine (64.3%) in the isCGM and BGM groups, respectively. The treatment regime for COVID-19 did not differ significantly between the two groups. There were no deaths among patients in either group.

Glycemic control and insulin dose

The blood glucose data during the first week after hospitalization are shown in Figure 1 and Supplementary Table S3 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*). The 4-point glucose data (before each meal and bedtime) using BGM were used to compare the glycemic control between isCGM and BGM (Supplement "Materials and methods"). Although the methylprednisolone therapy regimen and severity of COVID-19 did not significantly differ between the isCGM and BGM groups, the mean blood glucose levels during the 7 days were significantly lower in the isCGM group than in the BGM group. The mean blood glucose levels were high on days 1–3 in both groups; however, after day 4, the blood glucose levels were significantly lower in the isCGM group than in the BGM group. In the isCGM group, more than 70% of glucose measurements were in the range of 70–180 mg/dL (3.9–10.0 mmol/L) after the sixth day while it was only 40.9 % in the BGM group. In patients using BGM, marked hyperglycemia (blood glucose level > 250 mg/dL) was observed in 59.9% during the first 3 days, with persisting hyperglycemia (blood glucose level > 180 mg/dL). No hypoglycemia was observed in the isCGM group, but hypoglycemia was observed in a few patients in the BGM group.

The total daily insulin doses during the first week after admission are shown in Figure 2 and Supplementary Table S4 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*). In patients using isCGM, the insulin dose significantly increased after methylprednisolone therapy was started, leading to better glycemic control in the isCGM group than in the BGM group. Patients using isCGM were treated with > 110 units/day (1.19 units/kg/day) of insulin on the third and fourth days after admission; however, hypoglycemia was not observed. The basal and bolus insulin levels increased, and the bolus insulin requirement was particularly prominent.

The use of isCGM improves glycemic management under methylprednisolone therapy

This is exploratory research showing that although it is difficult to control hyperglycemia in patients with diabetes receiving methylprednisolone therapy for severe COVID-19, using isCGM enables better glycemic control through timely and adequate increases in the insulin dose without causing hypoglycemia.

Intravenous insulin is recommended for glycemic control in critically ill patients (*7*). However, frequent patient contact is required to monitor blood glucose levels. There is a need for alternative methods of glycemic control, particularly during a pandemic with limited resources for intensive care unit beds and PPE, to reduce the risk of exposure for healthcare

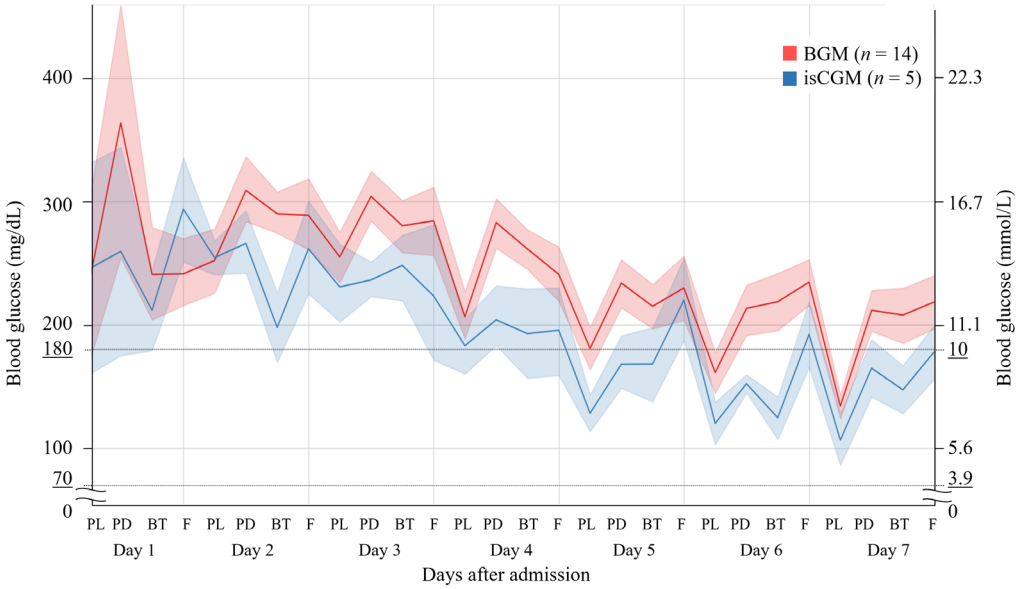

Figure 1. Dynamic trajectories of median blood glucose levels during the first week of hospitalization in patients using intermittently scanned continuous glucose monitoring (isCGM) or blood glucose monitoring (BGM) (red). Point-of-care glucose levels were assessed at fasting (F), pre-lunch (PL), pre-dinner (PD), and at bedtime. The target range of the blood glucose level is between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) (underlined). The interquartile ranges for median blood glucose levels are presented as shaded regions.

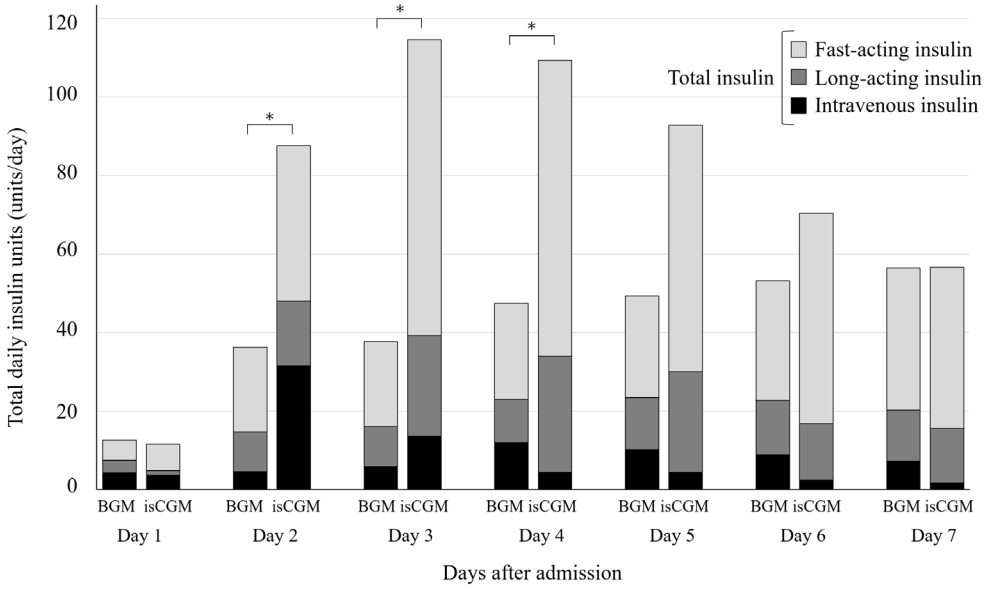

Figure 2. Bar graph showing the mean total daily insulin dose (TDI) in the blood glucose monitoring (BGM) group and intermittently scanned continuous glucose monitoring (isCGM) group during the first week of hospitalization. TDI includes subcutaneous injection of fast-acting insulin (shown in light gray), long-acting insulin (shown in dark gray), and intravenous insulin injection (shown in black). $^{*}p < 0.05$ according to the Student *t*-test.

workers caring for patients with COVID-19 (*8*). Use of CGM devices are recommended for these purposes (*9*). Several reports have shown that patients with severe COVID-19 require higher than usual insulin requirements, and glucocorticoids may significantly affect insulin requirements (*8,10*). Methylprednisolone, which is an intermediate-acting glucocorticoid, imparts a hyperglycemic effect 4 hours after administration, which peaks at 8 hours and decreases at 12–16 hours. This effect disappears by the following day. Therefore, methylprednisolone therapy causes drastic fluctuations in blood glucose levels throughout the day, whereas dexamethasone (a long-acting glucocorticoid) has a slow-acting hyperglycemic effect that continues to the next day (*11*). Thus, insulin delivery that enables rapid adaptation to dramatic changes in blood glucose levels

is required. In our study, elevated blood glucose levels caused by meals and intravenous methylprednisolone were continuously monitored in patients using isCGM. This enabled timely and adequate adjustment of insulin doses. Our observation indicates that using CGM is an effective way to attain good and safe glycemic control, especially in patients with severe COVID-19.

COVID-19 infection increases insulin resistance through the activation of inflammatory cells, which affect insulin-sensitive organs such as skeletal muscle and liver. Further, the induced cytokine storm blocks insulin signaling (*12*). With this background in patients with COVID-19, the use of glucocorticoids further reduces peripheral insulin sensitivity, increases hepatic gluconeogenesis, and inhibits pancreatic insulin production and secretion (*13-15*). Thus, in patients with diabetes who require glucocorticoid therapy for severe COVID-19, an adequate amount of insulin needs to be used to avoid severe hyperglycemia.

In our observation, insulin requirements began to decrease after the fourth day of hospitalization. Since insulin requirements may change daily due to the patient's clinical conditions and methylprednisolone doses change in patients with severe COVID-19 with diabetes (*16*), careful attention should be paid to the appropriate timing of insulin dose adjustment. Although methylprednisolone therapy initially causes hyperglycemia, it also blocks the cytokine storm and can improve insulin resistance (*17*). Furthermore, a recent study showed that tocilizumab used in patients with severe COVID-19 improves insulin resistance by targeting the interleukin-6 pathway (*18*). This may also be true in patients with diabetes, however, further studies are required. Tocilizumab is less effective when administered under hyperglycemic conditions (*19*), therefore, achieving good glycemic control during the initial hospitalization stage of COVID-19 infection is extremely important.

Four of the five patients using isCGM scanned the sensor with their smartphones, allowing their diabetologists to remotely monitor their trends of blood glucose levels through the cloud system. One patient in the present study did not possess a smartphone, and a reader device was provided to the patient to scan the sensor. Since changes in blood glucose levels can be monitored without increasing the frequency of POC testing, isCGM is beneficial in reducing the exposure of healthcare staff to infected patients (*5*). In April 2020, the Food and Drug Administration stated that it would not object to the use of CGM devices in the inpatient setting during the pandemic (*20*). We strongly emphasize the need for CGM, including isCGM, to be implemented in the hospital setting for effective and safe glycemic control during hospitalization, especially in patients with diabetes who require glucocorticoid therapy or those who require strict glycemic control.

This study has some limitations. First, the sample size was small, and only five patients used isCGM. Nevertheless, we believe that these five cases can provide important information in the situation of the COVID-19 pandemic. Second, the selection of patients using isCGM was left to the decision of the diabetologist in charge, and there were no definite criteria. Thus, there may be bias to consider, although there were no apparent differences in the history of diabetes control, severity of COVID-19 infection, and treatment regimen between the two groups. Therefore, we believe that our results warrant attention.

Conclusion

We show that despite the extreme difficulty of controlling hyperglycemia in severely ill patients with COVID-19 receiving methylprednisolone therapy, isCGM can be safely and effectively used to achieve better glycemic control and minimize the possible risks to healthcare workers during the COVID-19 pandemic. The use of isCGM will lead to good glycemic control with decreased time in hyperglycemia and hypoglycemia in patients with severe infectious diseases. Our next task will be to build a structured system, including staff education and technical support, for the safe implementation of isCGM for inpatient glycemic control.

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