Original Article

SAGE Open Medicine

SAGE Open Medicine
Volume 12: 1–11

DOI: 10.1177/20503121241238148
journals.sagepub.com/home/smo
Sage

Optimal initial insulin dosage for managing steroid-induced hyperglycemia in hospitalized COVID-19 patients: A retrospective single-center study

Nuttavadee Ketaroonrut, Sasisopin Kiertiburanakul and Chutintorn Sriphrapradang

Abstract

Objectives: To determine the optimal initial insulin dosage for controlling hyperglycemia in COVID-19 patients receiving steroids, an area with limited data.

Methods: We retrospectively analyzed 156 COVID-19 patients with steroid-induced hyperglycemia treated with insulin. Patients were categorized by their total daily dose of subcutaneous insulin therapy when starting dexamethasone ⩾6 mg/day or equivalent dose of glucocorticoid: Group A (⩽0.29 units/kg), Group B (0.3–0.49 units/kg), Group C (0.5–0.69 units/kg), and Group B (⩾0.7 units/kg). Treatment failure was defined as mean blood glucose level > 280 mg/dL for two consecutive days after initiating insulin or any blood glucose ⩾ 400 mg/dL.

Results: The mean age was 64 ± 14 years, with 50% male, and a mean body mass index of 26.9 ± 6.9 kg/m^2. Most had preexisting type 2 diabetes (62%). Mean admission blood glucose and HbA1c were 233 ± 112 mg/dL and 7.8 ± 2.3%, respectively. Group A had the lowest HbA1c (6.7 ± 1.2%), while group D had the highest (9.8 ± 2.5%). Median daily dexamethasone dosage or equivalent was 36 (IQR 16.72) mg, with no significant differences in among groups. Group A had the lowest treatment failure rate. There were no significant differences in treatment failure rate between Groups B, C, and D. Additionally, there were no statistically significant differences in mean BG across the groups: Group A 232 ± 42 mg/dL, Group B 247 ± 57 mg/dL, Group C 247 ± 61 mg/dL, and Group D 227 ± 67 mg/dL ($p = 0.2$). Group D had a significantly higher rate of level 1 hypoglycemia ($p = 0.008$), while no differences in clinically significant hypoglycemia (level 2 or 3) were observed between groups.

Conclusions: Among patients requiring TDD ⩾ 0.3 units/kg/day, there was no significant difference in treatment failure rate between Groups B, C, and D. Group D had the highest rate of level 1 hypoglycemia. This initial insulin dosage for hospitalized COVID-19 patients on high-dose steroid therapy should be personalized.

Keywords

Complications, dexamethasone, diabetes mellitus, glucocorticoids, hospitalization, inpatients, SARS-CoV-2

Date received: 7 September 2023; accepted: 22 February 2024

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus, which emerged as a global pandemic in December 2019. Patients with COVID-19 can experience a wide range of symptoms, from mild to severe, and may develop life-threatening complications, such as acute respiratory distress syndrome. The therapeutic approach for COVID-19 includes the use of antiviral agents, anticoagulants, and anti-inflammatory drugs, such as glucocorticoids and immunosuppressants, with the aim of improving symptoms and reducing mortality rates.[1] Notably, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial demonstrated that

Faculty of Medicine, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Corresponding author:
Chutintorn Sriphrapradang, Faculty of Medicine, Department of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchatewi, Bangkok 10400, Thailand.
Email: chutins@gmail.com

administering oral or intravenous dexamethasone at a daily dose of 6 mg for up to 10 days led to reduced mortality in patients requiring therapy with supplemental oxygen or invasive mechanical ventilation.[2]

Glucocorticoids, commonly known as steroids, are widely prescribed in clinical practice due to their potent anti-inflammatory and immunosuppressive properties.[3,4] In this paper, the term "steroid" refers to glucocorticoids. In COVID-19 patients with impaired immunity, an exaggerated immune response triggers a cytokine storm, leading to severe inflammation and lung injury, potentially resulting in multiorgan failure and mortality.[5] A meta-analysis in COVID-19 patients revealed a high incidence of acute respiratory distress syndrome (ARDS) cases at 19.5%, with a mortality rate of 5.5%.[6] The anti-inflammatory and immunosuppressant effects of steroids offer benefits to patients with ARDS by reducing the cytokine storm and serving as a bridge for initiating specific antiviral or disease-modifying treatments.[7] Several meta-analyses have demonstrated that steroid treatment reduces mortality rates in severe COVID-19 cases.[8–10] However, it is important to note that steroids increase the risk of hyperglycemia, even in patients without preexisting diabetes.[11–13]

Steroid-induced hyperglycemia develops through a complex process that involves an increase in hepatic gluconeogenesis and promotion of adipose lipolysis, followed by the development of whole-body insulin resistance, as well as impaired insulin synthesis and secretion by pancreatic beta cells.[12] The prevalence of steroid-induced hyperglycemia is reported to range from 56% to 86% in individuals with and without preexisting diabetes.[14,15] Moreover, steroids can trigger hyperosmolar hyperglycemic state and diabetic ketoacidosis, especially in patients with preexisting diabetes.[16–20]

Hyperglycemia in hospitalized patients has been associated with unfavorable outcomes, including increased mortality, higher infection rates, and prolonged hospital stays.[21–23] Hyperglycemia also promotes viral replication, increases viral load, and extends viral shedding.[24,25] Individuals with diabetes tend to have a greater release of proinflammatory cytokine, compromised host immune responses, and endothelial dysfunction, potentially leading to a more severe clinical response to COVID-19.[26–28] The poor glycemic control in critically ill patients is closely linked to more severe COVID-19 disease.[29–31] Well-controlled blood glucose (BG) has been correlated with improved survival rates for COVID-19 patients with type 2 diabetes.[30] This evidence has emphasized the importance of monitoring BG levels and glycemic control in COVID-19 patients.

The management of steroid-induced hyperglycemia in the hospital settings, particularly in COVID-19 patients, remains a subject of limited research.[32,33] Existing guidelines by the American Diabetes Association (ADA), Joint British Diabetes Societies, and the Endocrine Society offer recommendations for managing hyperglycemia secondary to steroid therapy.[34–36] According to the ADA guideline, glycemic targets and management for patients with steroid-induced hyperglycemia do not differ from those with any other type of diabetes.[34] In the statement by the Endocrine Society, it is recommended that patients treated with glucocorticoids who develop hyperglycemia should be managed with a basal/bolus insulin regimen, starting at a dose of 0.3–0.5 units/kg/day.[37] However, these recommendations primarily rely on expert opinion rather than evidence-based data.[38,39] Treatment with a computerized algorithm-based system of subcutaneous insulin has demonstrated efficacy and safety in managing steroid-induced hyperglycemia.[40] This study aimed to retrospectively analyze glycemic outcomes in hospitalized COVID-19 patients with steroid-induced hyperglycemia to evaluate the efficacy of different initial insulin dosages.

Methods

Study design and patient selection

We conducted a retrospective review of electronic medical records of COVID-19 patients (ICD-10-CM code U07.1) admitted to Ramathibodi Hospital between 1 August 2020 and 30 September 2021, who were treated with insulin therapy during their hospital stay. The study subjects included COVID-19 patients who received a daily dexamethasone dosage of $\geqslant$6 mg or an equivalent dose of glucocorticoid as part of the COVID-19 treatment protocol and developed hyperglycemia (defined as having random BG $>$ 200 mg/dL at least once) that required insulin therapy during their admission. COVID-19 diagnosis was confirmed by reverse transcription-polymerase chain reaction. Insulin therapy included a regimen with basal insulin only, as well as a combination of basal and bolus insulin administered through multiple daily injections or a twice-daily premixed insulin regimen. Basal insulin included neutral protamine Hagedorn (NPH, Insulatard, Novo Nordisk); glargine U100 (Lantus, Sanofi); glargine U300 (Toujeo, Sanofi); and degludec (Tresiba, Novo Nordisk). Bolus insulin included regular insulin (Actrapid, Novo Nordisk) and rapid-acting insulin analogs (insulin aspart, Novorapid, Novo Nordisk; lispro, Humalog, Eli Lilly; and glulisine, Apidra, Sanofi). Premixed insulin included premixed human insulin (30% regular insulin and 70% NPH insulin, Mixtard 70/30, Novo Nordisk) and premixed insulin analogs (30% insulin aspart and 70% neutral protamine aspart, NovoMix 70/30, Novo Nordisk; 25% insulin lispro and 75% neutral protamine lispro, HumalogMix 75/25, Eli Lilly), as well as coformulation (30% insulin aspart and 70% insulin degludec, Ryzodeg 70/30, Novo Nordisk). The decision regarding glucocorticoid dosage was based on the best clinical evidence available from various clinical trials, including RECOVERY,[2] CODEX,[41] and Meth-COVID trials.[42]

We excluded patients aged $<$18 years old, patients with type 1 diabetes mellitus, pregnant women, those requiring total parenteral nutrition or tube feeding, those allergic to

insulin, those with decompensated or end-stage chronic organ dysfunction (e.g., decompensated cirrhosis, end-stage renal disease requiring dialysis), patients who were unable to use subcutaneous insulin due to hemodynamically instability, or those immediately admitted to the intensive care unit (ICU), those who received other hypoglycemic agents other than insulin, those with diabetic ketoacidosis or hyperosmolar hyperglycemic state[43] at admission, those with incomplete medical records (e.g., transfer to another hospital), and patients with a duration of hospital stay <3 days. We also excluded patients who receive only correctional insulin. The attending physicians primarily adjusted the insulin dosage in an attempt to achieve glycemic targets within the range of 70–180 mg/dL. In cases of challenging glycemic control, supervision was provided by endocrine specialists to manage BG levels.

We divided patients into four groups according to total daily dose (TDD) of insulin treatment during hospitalization on the first day of insulin initiation: Group A ⩽0.29 units/kg, Group B 0.3–0.49 units/kg, Group C 0.5–0.69 units/kg, and Group B ⩾0.7 units/kg. TDD of insulin included basal, bolus, and correctional insulin. For patients with preexisting insulin therapy, the first day of insulin initiation was considered from the time of hospitalization. At admission, the baseline characteristics (e.g., age, gender, body mass index, diabetic status, BG, and creatinine) collected at admission were recorded for each group.

Outcome measures

We analyzed all preprandial and bedtime capillary BG readings obtained and recorded in the electronic medical record during the 3 days following initiation of insulin therapy. We calculated the mean BG concentration and the percentage of BG values that deviated from the glycemic target range. Treatment failure to hyperglycemia was defined as either a mean BG level >280 mg/dL for two consecutive days after the first day of initiation of insulin therapy or any BG level ⩾400 mg/dL.[44] Hemoglobin A1c (HbA1c) levels were measured on the first day of hospitalization.

Hypoglycemic events (BG <70 mg/dL) were classified as follows: hypoglycemia "alert" value (level 1)—BG <70 mg/dL and ⩾54 mg/dL, clinically significant hypoglycemia (level 2)—BG <54 mg/dL), and severe hypoglycemia (level 3)—a severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia.[45] In addition, the occurrence of BG <40 mg/dL was assessed and considered as severe hypoglycemia, consistent with the definition used in many randomized clinical trials.[44,46]

The primary end point was to assess the differences in glycemic control between treatment groups, measured by the treatment failure rates. Secondary outcomes included differences in mean daily BG concentration during hospitalization between treatment groups, BG values falling within the target ranges, episodes of severe hyperglycemia (BG >240 mg/dL) after the first day of treatment),[44] the number of hypoglycemic events, and complications such as acute respiratory failure requiring invasive mechanical ventilation, transfer to an ICU, and hospital mortality. Additionally, univariate and multivariate analyses were conducted to identify factors that associated with treatment failure to hyperglycemia. Variables that demonstrated statistical significance in the univariate analyses were subsequently included in a multivariate analysis.

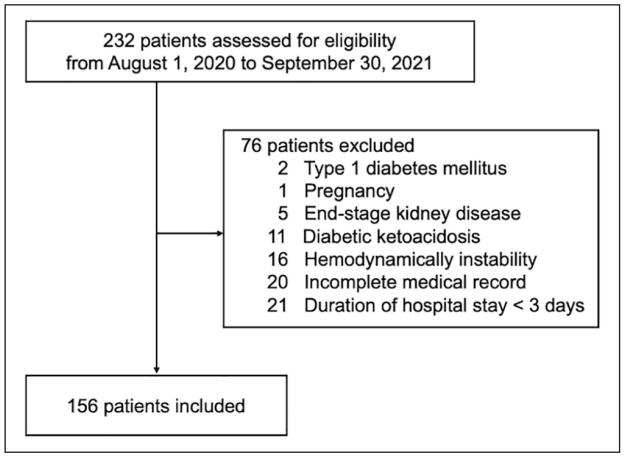

Figure 1. Study flowchart.

Statistical analyses

Categorical variables are expressed as counts and percentages. Continuous variables with normal distribution are presented as means and standard deviations, while non-normally distributed variables were reported as medians and interquartile ranges, as appropriate. The sample size was not calculated, as this study represents the first of its kind examining insulin treatment for steroid-induced hyperglycemia in COVID-19 patients. The differences in glycemic control among the groups were assessed using the Chi-squared, one-way analysis of variance, or Kruskal–Wallis tests, with post hoc multiple comparisons. Logistic regression analysis was used to investigate the association of variables with treatment failure to hyperglycemia. Univariate analysis is used to select variables for multivariate analysis, using a cutoff p-value of <0.2. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using STATA software version 17.0 (Stata Corp LLC, College Station, TX, USA).

Results

After exclusions (Figure 1), the study included a total of 156 patients, with a mean age of 64 ± 14 years, and 50% of them were male. The mean body mass index was 26.9 ± 6.9 kg/m^2.

Patients were classified into four groups based on their initial TDD of insulin: Group A (⩽0.29 units/kg/day, $n=79$), Group B (0.3–0.49 units/kg/day, $n=33$), Group C (0.5–0.69 units/kg/day, $n=27$), and Group D (⩾0.7 units/kg/day, $n=17$). The maximum TDD of insulin was 1.66 units/kg/day.

Baseline characteristics, including age, sex, body weight, body mass index, serum creatinine, and steroid dosage, were similar among the groups (Table 1). The majority of the patients (67%) were diagnosed with type 2 diabetes mellitus, with the highest prevalence observed in Group D. The mean admission BG and HbA1c levels were 233 ± 112 mg/dL and 7.8 ± 2.3%, respectively. HbA1c levels at admission were lowest in group A (6.7 ± 1.2%) and highest in group D (9.8 ± 2.5%). Serum creatinine levels were also similar across the groups. All cohorts received high-dosage glucocorticoids as part of the COVID-19 protocol, including dexamethasone (55%), methylprednisolone (45%), or other agents (0.6%). The median daily dexamethasone dosage or equivalent was 36 (IQR 16, 72) mg, and there was no significant difference among the groups. The TDD of insulin is shown in Table 1. The main proportion of insulin used was basal insulin. No patient receiving only correctional insulin or basal insulin was included in the study.

The glycemic outcomes are presented in Table 2.A total number of 1270 fingerstick BG readings were recorded during the 3-day study. The number of fingerstick BG readings per day did not differ between the TDD groups. The number of the proportion of treatment failure was lowest in Group A. Among patients requiring TDD ⩾0.3 units/kg/day, no significant differences were observed in the treatment failure rate between Groups B, C, and D. Furthermore, during the 3-day study period following the initiation of insulin therapy, there were no statistically significant differences in mean BG levels across the groups: Group A 232 ± 42 mg/dL, Group B 247 ± 57 mg/dL, Group C 247 ± 61 mg/dL, and Group D 227 ± 67 mg/dL ($p=0.2$). Despite the lack of significant difference, Group D showed a higher number of episodes of achieving BG concentrations between 70 and 180 mg/dL for 3 days after insulin treatment.

Hypoglycemic events (BG < 70 mg/dL) occurred in 10 events (0.8%) of all BG readings. A significant difference in rate of hypoglycemic events (BG < 70 mg/dL) was observed between groups, with Group D exhibiting the highest rate ($p=0.008$). Three patients had level 2 hypoglycemia (BG < 54 mg/dL) in this study. There are no significant differences in clinically significant hypoglycemia (level 2 or 3) were observed between groups (Group A: $n=1$, Group B: $n=1$, Group C: $n=0$, and Group D: $n=1$, $p=0.51$). No patient developed severe hypoglycemia with BG < 40 mg/dL.

There were no differences among groups in the frequency of hospital complications, including acute respiratory failure that necessitated invasive mechanical ventilation, transfer rates to the ICU, and mortality.

The univariate and multivariate analyses of variables associated with treatment failure are presented in Table 3. In the multivariate analysis, a significant association with treatment failure persisted for the TDD of insulin at 0.3–0.49 U/kg (Table 3).

Discussion

This retrospective single-center analysis of COVID-19 patients with steroid-induced hyperglycemia compared the efficacy of glycemic control, hypoglycemic events, and hospital complications between four different groups of patients receiving varying TDD of insulin. Our study found that among patients who require a TDD of ⩾0.3 units/kg/day of insulin, those who received a TDD ⩾0.7 units/kg/day of insulin experienced a similar rate of treatment failure to hyperglycemia when compared with other TDD groups, accompanied by an increase in nonclinically significant hypoglycemia.

The link between hyperglycemia in hospitalized patients, regardless of their diabetic status, and an elevated risk of prolonged hospitalization, complications, and mortality has been well established.[47] There are extensive data supporting the importance of hyperglycemia management among hospitalized patients.[34,36] Nevertheless, achieving glycemic targets may prove challenging, particularly in patients undergoing steroid treatment. Patients with type 2 diabetes mellitus receiving steroids may encounter difficulties in attaining glycemic targets even with higher insulin dosage.[48,49] The Endocrine Society Clinical Practice Guidelines recommend a starting daily insulin dose of 0.3–0.5 units/kg for hospitalized patients with hyperglycemia on steroids.[37] During the COVID-19 pandemic, Diabetes UK published guidance for the management of dexamethasone-induced hyperglycemia (BG > 216 mg/dL) and recommended initiating the use of isophane insulin (i.e., neutral protamine hagedorn or NPH) at 0.3 units/kg, with a more resistant sliding scale.[50] However, these recommendations are based on limited evidence and expert opinions. A retrospective study of cancer patients receiving high-dose steroids as part of chemotherapy and having two BG readings >250 mg/dL found that the group initiating a TDD of insulin at 1–1.2 units/kg/day as multiple-dose insulin regimen achieved better glycemic control.[51] The evidence from randomized trials in steroid-induced hyperglycemia supports the safety of hypoglycemia, even when initiating a daily insulin dosage of 0.5 units/kg, which is at the higher end of the recommended dosing range for insulin-naïve patients.[52] In addition, another randomized trial addressing steroid-induced hyperglycemia in patients admitted with pulmonary diseases, such as chronic obstructive pulmonary disease, asthma exacerbation, and pneumonia, and receiving high-dose steroids, reported that the risk of hypoglycemia remains low when using an initial daily insulin dosage of 0.51 units/kg.[53] Continuous glucose

Table 1. Baseline characteristics.

Baseline characteristics	All ($n=156$)	Group A (TDD ⩽0.29 U/kg, $n=79$)	Group B (TDD 0.3–0.49 U/kg, $n=33$)	Group C (TDD 0.5–0.69 U/kg, $n=27$)	Group D (TDD ⩾0.7 U/kg, $n=17$)	p-Value
Age, years	64 ± 14	65 ± 13	65 ± 12	62 ± 15	59 ± 14	NS
Male, n (%)	78 (50%)	43 (54%)	13 (39%)	12 (44%)	10 (59%)	NS
Body weight, kg	68.9 ± 17.5	68.1 ± 18.2	68.2 ± 13.7	68.8 ± 20.5	74.8 ± 15.8	NS
BMI, kg/m^2	26.9 ± 6.9	26.5 ± 6.9	26.9 ± 5	27.2 ± 9.3	28.6 ± 5.4	NS
Serum creatinine, mg/dL	0.98 ± 0.6	0.93 ± 0.6	1.11 ± 0.7	0.97 ± 0.5	0.97 ± 0.4	NS
History of DM*, n (%)						<0.05
Type 2 DM	105 (67%)	38 (48%)	27 (82%)	23 (85%)	17 (100%)	
Prediabetes	43 (28%)	34 (43%)	6 (18%)	3 (11%)	0 (0%)	
None	8 (5%)	7 (9%)	0 (0%)	1 (4%)	0 (0%)	
Pre-existing insulin therapy	22 (14.1%)	6 (7.6%)	6 (18.2%)	5 (18.5%)	5 (29.4%)	NS
HbA1c at admission						
HbA1c, %	7.8 ± 2.3	6.7 ± 1.2	7.7 ± 1.8	9.4 ± 3	9.8 ± 2.5	<0.05
HbA1c ⩾7%, n (%)	77 (49%)	23 (29%)	19 (57%)	20 (74%)	15 (88%)	<0.05
Admission BG, mg/dL	233 ± 112	194 ± 81	249 ± 100	273 ± 151	321 ± 122	<0.05
Steroid therapy						
Dexamethasone dosage or equivalent, mg/d	36 (IQR 16, 72)	31 (IQR 14, 69)	52 (IQR 20, 83)	32 (IQR 18, 46)	73 (IQR 16, 83)	NS
Types of steroids, n (%)						NS
Dexamethasone	85 (55%)	47 (59%)	16 (48%)	16 (59%)	6 (35%)	
Methylprednisolone	70 (45%)	31 (39%)	1 (52%)	11 (41%)	11 65%)	
Prednisolone	1 (0.6%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	
Insulin regimens, n (%)						
Basal-bolus	130 (83.3%)	78 (98.7%)	27 (81.8%)	16 (59.3%)	9 (52.9%)	<0.05
Premixed insulin	26 (16.7%)	1 (1.3%)	6 (18.2%)	11 (40.7%)	8 (47.1%)	<0.05

BG, blood glucose; BMI, body mass index; DM, diabetes mellitus; IFG, impaired fasting glucose; HbA1c, hemoglobin A1c; NS, nonsignificance; TDD, total daily dose; U, unit(s).
*The history of DM was obtained through history taking and medical record reviews. This included cases of undiagnosed DM determined by admission HbA1c diagnosis.

Table 2. Glycemic outcomes, hypoglycemic events, insulin therapy, and hospital complications.

Variables	Initial total insulin daily dose of insulin				*p*-Value
	Group A (TDD ⩽0.29 U/kg, *n* = 79)	Group B (TDD 0.3–0.49 U/kg, *n* = 33)	Group C (TDD 0.5–0.69 U/kg, *n* = 27)	Group D (TDD ⩾0.7 U/kg, *n* = 17)	
Treatment failure*, *n* (%)	15 (19%)	17 (52%)	10 (37%)	5 (29%)	0.006
Glycemic outcomes					
BG levels D1-3, mg/dL	232 ± 42	247 ± 57	247 ± 61	227 ± 67	NS
BG levels D2-3, mg/dL	225 ± 48	240 ± 60	232 ± 63	206 ± 60	0.2
BG levels at D1, mg/dL	235 ± 55	258 ± 70	276 ± 82	273 ± 92	0.02
BG levels at D2, mg/dL	231 ± 52	247 ± 69	238 ± 69	220 ± 79	NS
BG levels at D3, mg/dL	219 ± 57	233 ± 67	226 ± 79	193 ± 56	NS
Episodes of BG 70-180 mg/dL D1-3, %	17 (IQR 0, 40)	14 (IQR 0, 42)	17 (IQR 0, 36)	20 (IQR 0, 56)	NS
Episodes of BG 140-180 mg/dL D1-3, %	13 (IQR 0, 29)	0 (IQR 0, 25)	10 (IQR 0, 17)	6 (IQR 0, 18)	NS
Episodes of BG >240 mg/dL D1-3, %	43 (IQR 20, 67)	50 (IQR 33, 83)	50 (IQR 29, 63)	33 (IQR 20, 60)	NS
Hypoglycemic events**					
Level 1 hypoglycemia, n	1	2	2	5	0.008
Level 2 hypoglycemia, n	1	1	0	1	NS
Level 3 hypoglycemia, n	0	0	0	0	—
BG < 40 mg/dL	0	0	0	0	-
No. of fingerstick BG readings per day	2.7 ± 0.9	2.8 ± 0.8	2.9 ± 0.8	3 ± 0.9	NS
Insulin therapy					
TDD of insulin D1-3, units	48.8 ± 33.8	99.1 ± 42.4	135.6 ± 61	217.5 ± 62.3	<0.05
TDD of insulin D1-3, U/kg	0.73 ± 0.46	1.45 ± 0.57	1.97 ± 0.66	2.96 ± 0.86	<0.05
TDD of insulin D1-3, U/kg/DEX 1 mg	0.04 ± 0.04	0.05 ± 0.05	0.09 ± 0.09	0.13 ± 0.16	<0.05
Proportion of basal insulin***, %	99 ± 7	89 ± 18	78 ± 18	67 ± 13	<0.05
Complications					
Need invasive mechanical ventilation, *n* (%)	9 (11%)	5 (15%)	1 (3.7%)	3 (18%)	NS
Transfer to ICU, *n* (%)	6 (8%)	4 (12%)	1 (4%)	1 (6%)	NS
Death, *n* (%)	14 (18%)	4 (12%)	3 (11%)	3 (18%)	NS

BG, blood glucose; D, day; ICU, intensive-care unit; TDD, total daily dose; U, unit(s).

*Treatment failure was defined as either a mean BG level > 280 mg/dL for two consecutive days after the first day of initiation of insulin therapy or any BG level ⩾ 400 mg/dL.

**Hypoglycemic events were classified as: hypoglycemia "alert" value (level 1, BG < 70 mg/dL and ⩾54 mg/dL), clinically significant (level 2, BG < 54 mg/dL), and severe hypoglycemia (level 3, severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia).[45]

***Proportion of basal insulin represents the proportion of TDD administered as basal insulin.

Table 3. Univariate and multivariate analyses of various variables and treatment failure.

Variables	Treatment failure*, *n* (%)		Univariate analysis		Multivariate analysis	
	Yes (*n* = 47)	No (*n* = 109)	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
TDD (U/kg)						
<0.29 U/kg	15 (18%)	64 (81%)	1	—	1	—
0.3–0.49 U/kg	17 (52%)	16 (48%)	4.53 (1.87, 10.98)	**0.001**	3.65 (1.40, 9.57)	**0.008**
0.5–0.69 U/kg	10 (37%)	17 (63%)	2.51 (0.96, 6.57)	**0.061**	1.85 (0.60, 5.75)	0.287
>0.7 U/kg	5 (29%)	12 (71%)	1.78 (0.54, 5.82)	0.341	1.09 (0.28, 4.19)	0.897
Gender						
Male	21 (45%)	57 (52%)	1	—	1	—
Female	26 (55%)	52 (48%)	1.35 (0.68, 2.7)	0.384	1.34 (0.63, 2.87)	0.452
DM history						
None	1 (2%)	7 (6%)	1	—	1	—
Prediabetes	6 (13%)	37 (34%)	1.14 (0.12, 10.94)	0.913	0.97 (0.10, 9.84)	0.981
Type 2 DM	40 (85%)	65 (60%)	4.31 (0.51, 36.32)	**0.179**	2.61 (0.27, 25.03)	0.406
Baseline HbA1c	—	—	1.14 (0.99, 1.32)	**0.076**	1.01 (0.82, 1.25)	0.904
Steroid dosage	—	—	1 (1, 1.01)	0.252	1.00 (1.00, 1.01)	0.341
Baseline fasting BG	—	—	1.01 (1, 1.01)	**0.078**	1.00 (1.00, 1.00)	0.785
Types of steroids						
Dexamethasone	26 (55%)	59 (54%)	1	—	—	—
Methylprednisolone	21 (45%)	49 (45%)	0.97 (0.49, 1)	0.937	—	—
Age	—	—	0.98 (0.96, 1.01)	0.353	—	—
BMI	—	—	1 (0.95, 1.05)	0.906	—	—
Serum creatinine	—	—	0.96 (0.53, 1.72)	0.881	—	—

BG, blood glucose; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HbA1c, hemoglobin A1c; no., number; OR, odds ratio; TDD, total daily dose; U, unit(s).

Bold letters in the univariate analysis imply variables for multivariate analysis, using a cutoff *p*-value of <0.2; in the multivariate analysis, a *p*-value of <0.05 is considered statistically significant.

*Treatment failure was defined as a mean BG level > 280 mg/dL after the first day of insulin therapy or BG level ⩾ 400 mg/dL at least once a day.

monitoring data in patients with type 1 diabetes who were administered steroids indicated that the TDD insulin needed to be raised by at least 30%.[54] In the present study, we observed that a TDD of insulin ranging from 0.3 to ⩾ 0.7 units/kg resulted in similar successful glycemic control. Rates of hypoglycemia were more frequent in the TDD of insulin ⩾ 0.7 units/kg, although they did not lead to clinically significant hypoglycemia. These findings provide support for recommending an initial insulin dosage in steroid-induced hyperglycemia to be initiated at 0.3–0.5 units/kg, in accordance with the current Endocrine Society Clinical Practice Guidelines.[37]

Our results need to be interpreted with caution as COVID-19 itself has been demonstrated to lead to higher rates of hyperglycemia and new-onset diabetes, even without steroid treatment.[55] Our study found that COVID-19 patients in the highest TDD group had a mean TDD of 1.01 ± 0.26 units/kg. COVID-19 patients may require higher doses of insulin than individuals with acute illness who are not affected by COVID-19. A small case series of COVID-19 patients with diabetes admitted to ICU reported extremely high insulin doses, with a mean insulin requirement of up to 2.2 units/kg/day during the peak inflammatory response.[56] The initial insulin dose and timing of insulin administration should be personalized based on the severity of hyperglycemia and the dosage of steroid therapy.[37] Continuous insulin infusion is considered an appropriate approach for managing cases of severe and difficult-to-control hyperglycemia.[37]

A rational approach to attain optimal glycemic control is to initiate basal insulin in a manner dependent on the patient's body weight and the dose of steroid administration. Expert recommendations suggest initiating basal insulin based on steroid dose, with the daily insulin dose increased by 0.1 units/kg for every 10 mg of prednisone (or its equivalent, such as dexamethasone 2 mg prescribed), up to a maximum of 0.4 units/kg.[13,57] Previous randomized trials have shown that adding isophane insulin (0.1–0.4 units/kg/day) based on steroid dose and oral intake to patients with diabetes who were already on a basal-bolus insulin regimen led to a significant improvement in glycemic control.[58,59]A retrospective study from an academic medical center provided valuable insights into optimal TDD of insulin based on steroid dosage, revealing optimal TDD insulin of 0.294, 0.257, and 0.085 units/kg for low-, medium-, and high-dose steroid subgroups, respectively.[60] Similarly, the optimal basal insulin doses per 10-mg prednisone were 0.215, 0.126, and 0.036 units/kg for the low-, medium-, and high-dose steroid subgroups, respectively.[60] Our study shows similar a TDD insulin-to-steroid ratio to previous research and expert guidance about 0.1 units/kg for dexamethasone 2 mg (equivalent

to prednisone 10 mg) in high-dose steroid usage (dexamethasone ⩾ 6 mg/day).

Another factor to consider regarding TDD insulin is the baseline HbA1c level. A retrospective study in COVID-19 patients demonstrated that those with higher HbA1c levels, particularly with HbA1c ⩾ 8%, experienced more significant steroid-induced hyperglycemia and required higher insulin doses.[61] This finding was consistent with our study, which observed that patients who required highest TDD also had the highest admission HbA1c levels.

A basal-bolus insulin regimen includes the administration of basal insulin given once or twice daily along with rapid-acting insulin given before meal, plus corrective doses of rapid-acting insulin is the preferred subcutaneous insulin regimen for inpatient glycemic management.[37,62] For steroid-induced hyperglycemia, the Endocrine Society recommended glycemic management with either isophane insulin-based insulin or basal-bolus regimens. Inpatient glycemic management with premixed human insulin therapy resulted in similar glycemic control but in significantly higher hypoglycemic rates compared with basal-bolus regimen.[63] On the contrary, an observational study revealed that the rate of hypoglycemia did not increase in hospitalized patients with type 2 diabetes using premixed insulin.[64,65] These findings may be explained by premixed insulin analog reduces the risk of hypoglycemia compared to human premixed insulin.[66] In our study, we observed a higher percentage of premixed insulin use compared to the basal-bolus regimen. During the peak of the COVID-19 pandemic, premixed insulin was considered an alternative option for insulin therapy to reduce infection exposure for health care professionals.

Additionally, the proportion of basal insulin was significantly higher than bolus insulin, as physicians opted for long-acting insulin prescriptions to reduce COVID-19 exposure risks. Considering steroid-induced insulin resistance and the prevalence of high postprandial hyperglycemia when high steroid doses are administered, there is often a need to increase bolus insulin doses, sometimes by as much as 40%–60% or even up to 75%, in addition to basal insulin.[38,51,67]

Due to the action of isophane insulin peaks at 4–6 h after administration, it is recommended to administer it concomitantly with intermediate-acting steroids (e.g., prednisone, prednisolone, methylprednisolone). For long-acting glucocorticoids such as dexamethasone or when using multidose or continuous glucocorticoid therapy, it may necessary to use long-acting basal insulin to effectively manage fasting BG levels.[45] The choice between glargine and isophane insulin as basal insulin for managing steroid-induced hyperglycemia in hospitalized patients remains a matter of debate. Previous studies, including both retrospective studies and randomized controlled trials, have suggested that both glargine and isophane insulin demonstrate equal effectiveness in managing steroid-induced hyperglycemia.[53,68]

One of the strengths of our study is the emphasis on the optimal TDD of insulin in COVID-19 patients receiving high-dose steroid treatment. This valuable information can play a crucial role in managing potential extreme cases in the future, particularly if new pandemic viruses emerge. However, it is important to acknowledge several limitations in our study. Firstly, the retrospective design introduces limitations to our findings. To address these limitations, prospective clinical trials should be conducted in the future. To achieve optimal glycemic targets, it is essential to focus not only on insulin initiation but also on the intensification of insulin therapy. Integrating algorithm protocols from previous studies into our results would prove beneficial for improving the glycemic management in cases of steroid-induced hyperglycemia.[32,33] Our sample size was small, and it was not calculated due to the lack of prior studies. Additionally, the results obtained from COVID-19 patients may not directly apply to non-COVID-19 patients with steroid-induced hyperglycemia. Currently, noninsulin therapies, such as DPP-4 inhibitors, have demonstrated safety in the hospitalized patients.[69] Our study excluded patients who were using noninsulin antihyperglycemic agents. Throughout the COVID-19 pandemic, physicians from diverse specialties have collaborated to provide patient care, but some of them may lack extensive experience in inpatient glycemic management. In some cases, consultant endocrinologists may not be readily available to take charge during the initial days of admission. This study was conducted before the emergence of other COVID-19 variants, including the Omicron variants.

Conclusions

In the present study, we observed that an initial TDD of insulin on Day 1 at ⩾ 0.7 units/kg/day did not result in significantly difference mean BG control or rates of treatment failure compared to other initial TDD groups. This initial insulin dosage for hospitalized COVID-19 patients undergoing high-dose steroid therapy should be personalized to individual needs.

Acknowledgements

The authors thank Chaiyawat Suppasilp and Sasiporn Sitthisorn from Department of Clinical Epidemiology and Biostatistics for statistical analysis suggestion. The abstract was presented at the ENDO 2023, in Chicago, Illinois.

Author contributions

NK and CS designed the study. All authors collected, analyzed, and interpreted the data. NK drafted the manuscript. All authors read, revised, and approved the final manuscript.

Data availability

The data sets generated and analyzed during this study are available from the corresponding author upon request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Ethical approval for this study was obtained from the Human Research Ethics Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (ethical approval number MURA 2021/927).

Informed consent

Informed consent was waived by the ethics committee due to the retrospective type of research.

Trial registration

Not applicable.

ORCID iD

Chutintorn Sriphrapradang https://orcid.org/0000-0001-8294-8601

References

1. Li G, Hilgenfeld R, Whitley R, et al. Therapeutic strategies for COVID-19: progress and lessons learned. *Nat Rev Drug Discov* 2023; 22: 449–475.
2. Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; 384: 693–704.
3. Fardet L, Petersen I and Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. *Rheumatology (Oxford)* 2011; 50: 1982–1990.
4. Benard-Laribiere A, Pariente A, Pambrun E, et al. Prevalence and prescription patterns of oral glucocorticoids in adults: a retrospective cross-sectional and cohort analysis in France. *BMJ Open* 2017; 7: e015905.
5. Montazersaheb S, Hosseiniyan Khatibi SM, Hejazi MS, et al. COVID-19 infection: an overview on cytokine storm and related interventions. *Virol J* 2022; 19: 92.
6. Zhu J, Ji P, Pang J, et al. Clinical characteristics of 3062 COVID-19 patients: a meta-analysis. *J Med Virol* 2020; 92: 1902–1914.
7. Raju R, V P, Biatris PS, et al. Therapeutic role of corticosteroids in COVID-19: a systematic review of registered clinical trials. *Futur J Pharm Sci* 2021; 7: 67.
8. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020; 324: 1330–1341.
9. Siemieniuk RA, Bartoszko JJ, Zeraatkar D, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020; 370: m2980.
10. Crichton ML, Goeminne PC, Tuand K, et al. The impact of therapeutics on mortality in hospitalised patients with COVID-19: systematic review and meta-analyses informing the European Respiratory Society living guideline. *Eur Respir Rev* 2021; 30: 210171.
11. Rhou YJJ, Hor A, Wang M, et al. Dexamethasone-induced hyperglycaemia in COVID-19: glycaemic profile in patients without diabetes and factors associated with hyperglycaemia. *Diabetes Res Clin Pract* 2022; 194: 110151.
12. Li JX and Cummins CL. Fresh insights into glucocorticoid-induced diabetes mellitus and new therapeutic directions. *Nat Rev Endocrinol* 2022; 18: 540–557.
13. Suh S and Park MK. Glucocorticoid-induced diabetes mellitus: an important but overlooked problem. *Endocrinol Metab (Seoul)* 2017; 32: 180–189.
14. Donihi AC, Raval D, Saul M, et al. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. *Endocr Pract* 2006; 12: 358–362.
15. Pichardo-Lowden AR, Fan CY and Gabbay RA. Management of hyperglycemia in the non-intensive care patient: featuring subcutaneous insulin protocols. *Endocr Pract* 2011; 17: 249–260.
16. Cagdas DN, Pac FA and Cakal E. Glucocorticoid-induced diabetic ketoacidosis in acute rheumatic fever. *J Cardiovasc Pharmacol Ther* 2008; 13: 298–300.
17. Alakkas Z, Alzaedi OA, Somannavar SS, et al. Steroid-induced diabetes ketoacidosis in an immune thrombocytopenia patient: a case report and literature review. *Am J Case Rep* 2020; 21: e923372.
18. Rahman SA, Karmakar A, Almustafa MM, et al. Preoperative steroids triggering diabetic ketoacidosis in the neurosurgical patient. *J Clin Anesth* 2018; 46: 33–34.
19. Cavataio MM and Packer CD. Steroid-induced diabetic ketoacidosis: a case report and review of the literature. *Cureus* 2022; 14: e24372.
20. Kang SH, Lee JY, Park HS, et al. Hyperglycemic hyperosmolar syndrome caused by steroid therapy in a patient with lupus nephritis. *J Korean Med Sci* 2011; 26: 447–449.
21. Krinsley JS, Egi M, Kiss A, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care* 2013; 17: R37.
22. Falciglia M, Freyberg RW, Almenoff PL, et al. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009; 37: 3001–3009.
23. Gracia-Ramos AE, Carretero-Gomez J, Mendez CE, et al. Evidence-based therapeutics for hyperglycemia in hospitalized noncritically ill patients. *Curr Med Res Opin* 2022; 38: 43–53.
24. Kohio HP and Adamson AL. Glycolytic control of vacuolar-type ATPase activity: a mechanism to regulate influenza viral infection. *Virology* 2013; 444: 301–309.
25. Fontana LM, Villamagna AH, Sikka MK, et al. Understanding viral shedding of severe acute respiratory coronavirus virus 2 (SARS-CoV-2): review of current literature. *Infect Control Hosp Epidemiol* 2021; 42: 659–668.
26. Cox RJ and Brokstad KA. Not just antibodies: B cells and T cells mediate immunity to COVID-19. *Nat Rev Immunol* 2020; 20: 581–582.

27. Stefan N. Metabolic disorders, COVID-19 and vaccine-breakthrough infections. *Nat Rev Endocrinol* 2022; 18: 75–76.
28. Li M, Wu X, Shi J, et al. Endothelium dysfunction and thrombosis in COVID-19 with type 2 diabetes. *Endocrine* 2023; 82(1): 15–27.
29. Bode B, Garrett V, Messler J, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. *J Diabetes Sci Technol* 2020; 14: 813–821.
30. Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and preexisting type 2 diabetes. *Cell Metab* 2020; 31: 1068–1077. e1063.
31. Klonoff DC, Messler JC, Umpierrez GE, et al. Association between achieving inpatient glycemic control and clinical outcomes in hospitalized patients with COVID-19: a multicenter, retrospective hospital-based analysis. *Diabetes Care* 2021; 44: 578–585.
32. Asiri AA, Alguwaihes AM, Jammah AA, et al. Assessment of the effectiveness of a protocol to manage dexamethasone-induced hyperglycemia among hospitalized patients with COVID-19. *Endocr Pract* 2021; 27: 1232–1241.
33. Karol AB, Viera N, Ogyaadu SJ, et al. A novel algorithm for the management of inpatient COVID-19 glucocorticoid-induced hyperglycemia. *Clin Diabetes* 2023; 41: 378–385.
34. ElSayed NA, Aleppo G, Aroda VR, et al. 16. Diabetes care in the hospital: standards of care in diabetes-2023. *Diabetes Care* 2023; 46: S267–S278.
35. Roberts A, James J, Dhatariya K, et al. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. *Diabet Med* 2018; 35: 1011–1017.
36. Korytkowski MT, Muniyappa R, Antinori-Lent K, et al. Management of hyperglycemia in hospitalized adult patients in non-critical care settings: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2022; 107: 2101–2128.
37. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2012; 97: 16–38.
38. Spanakis EK, Shah N, Malhotra K, et al. Insulin requirements in non-critically ill hospitalized patients with diabetes and steroid-induced hyperglycemia. *Hosp Pract (1995)* 2014; 42: 23–30.
39. Aberer F, Hochfellner DA, Sourij H, et al. A practical guide for the management of steroid induced hyperglycaemia in the hospital. *J Clin Med* 2021; 10: 2154.
40. Aberer F, Mader JK, Holzgruber J, et al. Feasibility and safety of using an automated decision support system for insulin therapy in the treatment of steroid-induced hyperglycemia in patients with acute graft-versus-host disease: a randomized trial. *J Diabetes Investig* 2019; 10: 339–342.
41. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* 2020; 324: 1307–1316.
42. Edalatifard M, Akhtari M, Salehi M, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur Respir J* 2020; 56: 2002808.
43. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; 32: 1335–1343.
44. Galindo RJ, Pasquel FJ, Vellanki P, et al. Degludec hospital trial: a randomized controlled trial comparing insulin degludec U100 and glargine U100 for the inpatient management of patients with type 2 diabetes. *Diabetes Obes Metab* 2022; 24: 42–49.
45. ElSayed NA, Aleppo G, Aroda VR, et al. 6. Glycemic targets: standards of care in diabetes-2023. *Diabetes Care* 2023; 46: S97–S110.
46. Pasquel FJ, Lansang MC, Khowaja A, et al. A randomized controlled trial comparing glargine U300 and glargine U100 for the inpatient management of medicine and surgery patients with type 2 diabetes: glargine U300 hospital trial. *Diabetes Care* 2020; 43: 1242–1248.
47. Umpierrez GE, Isaacs SD, Bazargan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; 87: 978–982.
48. Burt MG, Drake SM, Aguilar-Loza NR, et al. Efficacy of a basal bolus insulin protocol to treat prednisolone-induced hyperglycaemia in hospitalised patients. *Intern Med J* 2015; 45: 261–266.
49. Chertok Shacham E, Kfir H, Schwartz N, et al. Glycemic control with a basal-bolus insulin protocol in hospitalized diabetic patients treated with glucocorticoids: a retrospective cohort study. *BMC Endocr Disord* 2018; 18: 75.
50. Rayman G, Lumb AN, Kennon B, et al. Dexamethasone therapy in COVID-19 patients: implications and guidance for the management of blood glucose in people with and without diabetes. *Diabet Med* 2021; 38: e14378.
51. Brady V, Thosani S, Zhou S, et al. Safe and effective dosing of basal-bolus insulin in patients receiving high-dose steroids for hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone chemotherapy. *Diabetes Technol Ther* 2014; 16: 874–879.
52. Radhakutty A, Stranks JL, Mangelsdorf BL, et al. Treatment of prednisolone-induced hyperglycaemia in hospitalized patients: Insights from a randomized, controlled study. *Diabetes Obes Metab* 2017; 19: 571–578.
53. Ruiz de Adana MS, Colomo N, Maldonado-Araque C, et al. Randomized clinical trial of the efficacy and safety of insulin glargine versus NPH insulin as basal insulin for the treatment of glucocorticoid induced hyperglycemia using continuous glucose monitoring in hospitalized patients with type 2 diabetes and respiratory disease. *Diabetes Res Clin Pract* 2015; 110: 158–165.
54. Bevier WC, Zisser HC, Jovanovic L, et al. Use of continuous glucose monitoring to estimate insulin requirements in patients with type 1 diabetes mellitus during a short course of prednisone. *J Diabetes Sci Technol* 2008; 2: 578–583.
55. Khunti K, Valabhji J and Misra S. Diabetes and the COVID-19 pandemic. *Diabetologia* 2023; 66: 255–266.
56. Wu L, Girgis CM and Cheung NW. COVID-19 and diabetes: insulin requirements parallel illness severity in critically unwell patients. *Clin Endocrinol (Oxf)* 2020; 93: 390–393.

57. Clore JN and Thurby-Hay L. Glucocorticoid-induced hyperglycemia. *Endocr Pract* 2009; 15: 469–474.
58. Khowaja A, Alkhaddo JB, Rana Z, et al. Glycemic control in hospitalized patients with diabetes receiving corticosteroids using a neutral protamine hagedorn insulin protocol: a randomized clinical trial. *Diabetes Ther* 2018; 9: 1647–1655.
59. Lakhani OJ, Kumar S, Tripathi S, et al. Comparison of two protocols in the management of glucocorticoid-induced hyperglycemia among hospitalized patients. *Indian J Endocrinol Metab* 2017; 21: 836–844.
60. Bajaj MA, Zale AD, Morgenlander WR, et al. Insulin dosing and glycemic outcomes among steroid-treated hospitalized patients. *Endocr Pract* 2022; 28: 774–779.
61. Gordon C, Kamel B, McKeon L, et al. Dexamethasone use and insulin requirements in coronovirus-19 (COVID-19) infection stratified by hemoglobin A1c. *Diabet Epidemiol Manag* 2023; 10: 100123.
62. Pasquel FJ, Lansang MC, Dhatariya K, et al. Management of diabetes and hyperglycaemia in the hospital. *Lancet Diabetes Endocrinol* 2021; 9: 174–188.
63. Bellido V, Suarez L, Rodriguez MG, et al. Comparison of basal-bolus and premixed insulin regimens in hospitalized patients with type 2 diabetes. *Diabetes Care* 2015; 38: 2211–2216.
64. Broz J, Janickova Zdarska D, Urbanova J, et al. Insulin management of patients with inadequately controlled type 2 diabetes admitted to hospital: titration patterns and frequency of hypoglycemia as results of a prospective observational study (hospital study). *Diabetes Ther* 2021; 12: 1799–1808.
65. Merkofer F, Struja T, Delfs N, et al. Glucose control after glucocorticoid administration in hospitalized patients—a retrospective analysis. *BMC Endocr Disord* 2022; 22: 8.
66. El Naggar N and Kalra S. Switching from biphasic human insulin to premix insulin analogs: a review of the evidence regarding quality of life and adherence to medication in type 2 diabetes mellitus. *Adv Ther* 2017; 33: 2091–2109.
67. Cheng YC, Guerra Y, Morkos M, et al. Insulin management in hospitalized patients with diabetes mellitus on high-dose glucocorticoids: management of steroid-exacerbated hyperglycemia. *PLoS One* 2021; 16: e0256682.
68. Dhital SM, Shenker Y, Meredith M, et al. A retrospective study comparing neutral protamine hagedorn insulin with glargine as basal therapy in prednisone-associated diabetes mellitus in hospitalized patients. *Endocr Pract* 2012; 18: 712–719.
69. Galindo RJ, Dhatariya K, Gomez-Peralta F, et al. Safety and efficacy of inpatient diabetes management with non-insulin agents: an overview of international practices. *Curr Diab Rep* 2022; 22: 237–246.