



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

## Diabetes &amp; Metabolic Syndrome: Clinical Research &amp; Reviews

journal homepage: [www.elsevier.com/locate/dsx](http://www.elsevier.com/locate/dsx)

## Original Article

## Daily glucose variation influenced by the use of corticosteroids in COVID-19 patients treated in Lima-Peru

Kennly J. Cardoza-Jiménez<sup>a,\*</sup>, Blanca Carranza-Zavala<sup>a</sup>, Katty Manrique-Franco<sup>b</sup>, Frank Espinoza-Morales<sup>c</sup>, Christian R. Mejia<sup>d</sup><sup>a</sup> Endocrinology Resident Physician – Hospital Nacional Arzobispo Loayza, Lima, Peru<sup>b</sup> Endocrine Assistant Physician - Hospital Nacional Arzobispo Loayza, Lima, Peru<sup>c</sup> Physician Nutrition Specialist - Center for Applied Diabetes Technologies (CAVIMEDIC), Lima, Peru<sup>d</sup> Translational Medicine Research Center, Universidad Norbert Wiener, Lima, Peru

## ARTICLE INFO

## Article history:

Received 17 May 2021

Received in revised form

21 June 2021

Accepted 23 June 2021

## Keywords:

Dexamethasone

Type 2 diabetes mellitus

COVID-19

Blood glucose

Hyperglycemia

Glycemic variability

## ABSTRACT

**Aim:** The pandemic has generated the need for COVID-19 patients to be treated as best as possible; however, the effect of these treatments on glycemic control has not yet been taken into account. This article aims to determine whether the daily variation of glucose is influenced by the use of corticosteroids in COVID-19 patients treated in Lima-Peru.

**Methodology:** A prospective cohort study was undertaken, in which glucose was measured four times a day in 53 patients hospitalized due to COVID-19. These values were associated with the use of corticosteroids and adjusted for other socio-educational variables, all by means of PA-GEE models.

**Results:** Nested multivariate analysis of daily glucose variation found that those using corticosteroids increased the daily average glucose as well as the first and last glucose measurements, this is, at 6am and 10pm, respectively (all p-values <0.026). An increase in glucose levels was also observed in those with diabetes (all p-values <0.001). In contrast, we found that there was a decrease in the last glucose measurement of the day in obese patients (p-value = 0.044).

**Conclusions:** The patients who used corticosteroids for the treatment of COVID-19 increased the average glucose per day, especially in the first and last measurement.

© 2021 Diabetes India. Published by Elsevier Ltd. All rights reserved.

## Introduction

The COVID-19 epidemic in Peru has one of the highest incidence and mortality rates worldwide [1], higher in people with previous pathologies, such as hypertension, obesity and type 2 diabetes mellitus (T2DM) [2,3].

The RECOVERY study demonstrated that the use of dexamethasone reduces mortality in one fifth of COVID-19 patients requiring oxygen therapy and in one third of patients requiring mechanical ventilation [4], through a possible decrease in the inflammatory cascade associated with the infection [5]. However, corticosteroid therapy increases insulin resistance, the endogenous glucose

production and the effect of counterregulatory hormones [6]. In addition, it has been reported that, in hospitalized patients with diabetes, the administration of corticosteroids produces an exacerbation of glycemic excursions [7,8] and generates sustained hyperglycemia [9]. On the other hand, stress mechanisms occur during hospitalization, which worsen glucose control in diabetic patients.

The association between hyperglycemia and adverse clinical outcomes in critical and non-critical patients is well established. In patients with diabetes, adequate glucose control reduces hospitalization days, multi-organ failure and mortality [10]. In this context, clinicians face great challenges in the therapy of hospitalized patients with COVID-19 and diabetes, since they receive dexamethasone on the one hand, with the aim of reducing inflammation, and on the other hand, they must achieve adequate glycemic control [11–13]. The present study seeks to determine whether daily glucose variation is influenced by the use of corticosteroids in patients treated for COVID-19 in Lima-Perú.

\* Corresponding author. Parque osores 108 dpto 1602, Pueblo Libre, Lima, Perú.

E-mail addresses: [kjossephej@gmail.com](mailto:kjossephej@gmail.com) (K.J. Cardoza-Jiménez), [bcarranza.zavala7034@gmail.com](mailto:bcarranza.zavala7034@gmail.com) (B. Carranza-Zavala), [manrique\\_fr@yahoo.es](mailto:manrique_fr@yahoo.es) (K. Manrique-Franco), [drespinozamorales@gmail.com](mailto:drespinozamorales@gmail.com) (F. Espinoza-Morales), [christian.mejia.md@gmail.com](mailto:christian.mejia.md@gmail.com) (C.R. Mejia).

## Materials and methods

### Study design and patient population

A prospective cohort study was conducted, in which daily capillary glucose was monitored four times, in 53 patients hospitalized due to SARS-COV-2 infection and who had received, as part of the treatment, dexamethasone during their hospitalization in COVID-19 wards of the National Hospital Arzobispo Loayza between July 1 and August 31, 2020. The study was approved by the Ethics Committee and the Teaching and Research Office of the National Hospital Arzobispo Loayza.

### Procedures and variables

The following data were collected: age, gender, weight and height, diabetes diagnosis, admission glucose, hemoglobin, hematocrit, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), creatinine, CRP and glycated hemoglobin (only for patients with T2DM). During dexamethasone administration, capillary glycemic was monitored four times a day (6 h, 12 h, 17 h and 22 h) and monitoring continued until 72 h after dexamethasone discontinuation. Those patients who presented with hyperglycemia were prescribed insulin treatment. All this information was inserted into a data collection form (generated *ad hoc* for this purpose); then, a first quality control of the data was carried out (by another researcher), after which the information was passed to the STATA statistical program (version 11.1), where a second quality control was carried out (by the statistician). After that, we proceeded with the analysis.

### Statistical analysis

For the construction of Table 1, the frequencies and percentages of the qualitative variables were obtained. For the description of the quantitative variables, they were evaluated with the Shapiro Wilk test and, according to the results, the best measure of central tendency and dispersion of each variable was obtained. For the construction of Tables 2 and 3, PA-GEE regression was used, taking into account the day of hospitalization as the variable time, the Gaussian family and the identity link function. With all these data, the coefficients, 95% confidence intervals (95%CI) and p-values were

obtained (values less than 0.05 were considered statistically significant, which is part of the criterion to pass the multivariate statistics).

## RESULTS

A total of 352 glucose measurements were obtained from the 53 patients. Of the patients, 56.6% were male, the median age was 57 (interquartile range: 52–67 years), 50.9% had diabetes and 58.5% did not have obesity. In the diabetic patients, the median BMI was 29.1 (interquartile range: 25.6–31.3). The other general characteristics are shown in Table 1.

When bivariate analysis was performed, it was found that those receiving corticosteroids presented with a daily variation in glucose at 6am (basal glucose increased by 23.9 mg/dl; 95% CI: 5.7–42.1; p-value = 0.010), 10pm (glucose increased by 46.5 mg/dl with respect of the initial value; 95%CI: 20.3–72.6; p-value<0.001) and in the daily average (basal glucose increased by 14.9 mg/dl; 95%CI: 1.7–28.1; p-value = 0.026). The other glucose values were not significantly altered. Table 2 and Fig. 1.

When nested multivariate analysis of daily glucose variation was performed, it was found that those using corticosteroids not only increased the daily average glucose, but also the first and last glucose measurement, that is at 6am and 10pm, respectively (all values  $p < 0.026$ ). In patients who had diabetes, there was also an increase in the daily average glucose and in the 6am and 10pm glucose. This increase was much more marked than in non-diabetics. (all values  $p < 0.001$ ). In the case of obese patients, there was a decrease in the last glucose measurement of the day (p-value = 0.044). Table 3 and Fig. 2.

## Discussion

In our findings, COVID-19 patients with a history of diabetes presented with hyperglycemia when being admitted to the hospital. Given the prescription of dexamethasone as part of the treatment during their hospitalization, it was evidenced that glucose values could double throughout the day (especially in the first and last measurements of the day); this was monitored with the glucose self-monitoring control profile. Similarly, non-diabetic patients receiving dexamethasone also increased their blood glucose levels, although to a lesser extent than diabetic patients.

Although the findings of the RECOVERY study [4] and a recent meta-analysis [14] support the indication of dexamethasone in patients with COVID-19 (requiring ventilation or oxygen requirement to reduce mortality); corticosteroid therapy with dexamethasone increases hyperglycemia [15]. Our findings suggest the personalized risk/benefit assessment of this drug in patients with diabetes and COVID-19.

In addition, corticosteroid therapy in patients with COVID-19 may precipitate the onset of diabetes in previously predisposed individuals with “de novo diabetes” [16]. These findings are extremely important, because in the current pandemic there are many cases that are complicated by having diabetes, and many of these patients use corticosteroid therapy.

It is reported that the values can double, this in a patient who has values of 120 mg/dL could mean the reaching of values of more than 200 mg/dL; also, if a patient has 200 or 300 of glycemia, added to an inadequate treatment, it could reach 400 or 600 mg/dL, respectively. This could be very serious if it cannot be adequately controlled. That is why clinical guidelines for the management of hospitalized patients with diabetes recommend the use of insulin therapy. In patients who do not require intensive care, the indication of a basal-bolus scheme for the management of hyperglycemia is suggested [10,17]. All this should be taken into account by the

**Table 1**  
General characteristics of the study population.

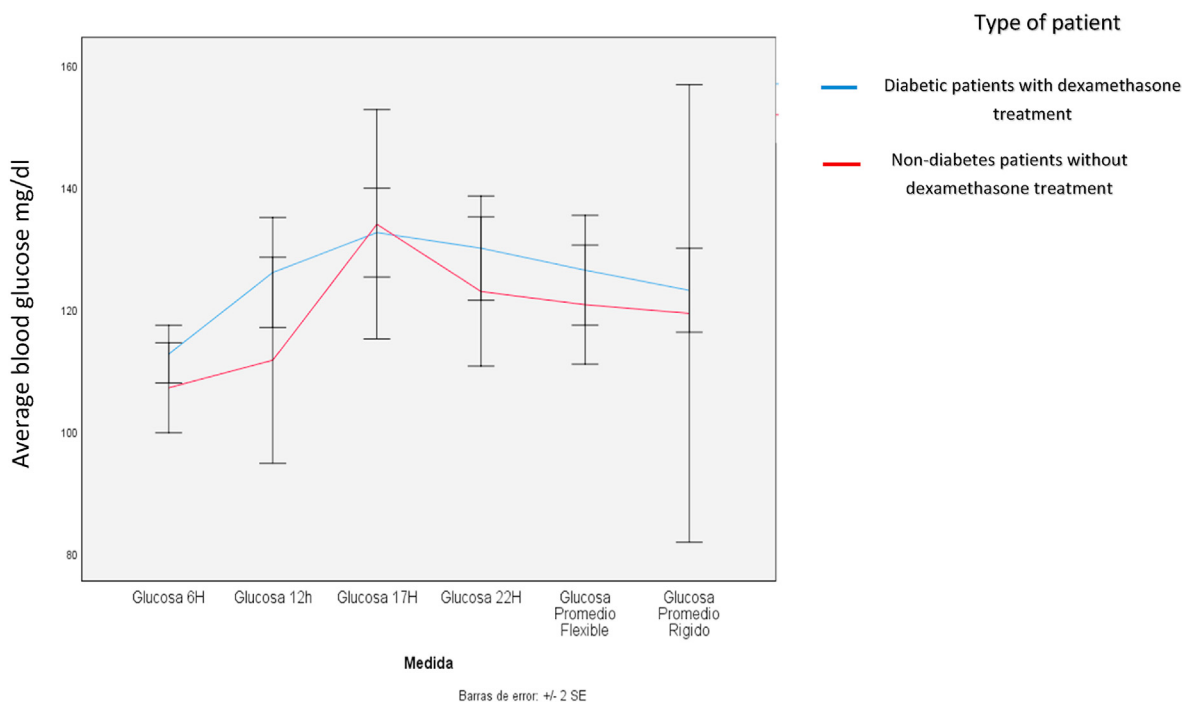
General characteristics	n (%)
Gender	
Male	30 (56,6)
Female	23 (43,4)
Age <sup>a</sup> (years old)	57 (52–67)
Diabetes	
Yes	27 (50,9)
No	26 (49,1)
BMI <sup>a</sup> (kg/m <sup>2</sup> )	29,1 (25,6–31,3)
Obesity	
Yes	22 (41,5)
No	31 (58,5)
Laboratory tests at hospital admission	
Serum glucose <sup>a</sup> (mg/dl)	140 (118–243)
Hemoglobin <sup>a</sup> (gr/dl)	13.7 (12.9–14.6)
GOT <sup>a</sup> (U/L)	34 (24–51)
GPT <sup>a</sup> (U/L)	45 (28–68)
CRP <sup>a</sup> (mg/dl)	11.1 (4.8–20.4)
Serum creatinine <sup>a</sup> (mg/dl)	0.75 (0.62–0.93)
HbA1c <sup>a</sup> (%) (N = 27)	9.7 (7.1–12)

<sup>a</sup> Median and interquartile ranges, HbA1c: in diabetic patients.

**Table 2**  
Bivariate analysis of glucose variation as hospitalization days passed according to the use of corticosteroids in patients with COVID-19.

Daily variation of glucose	Basal value	Bivariate analysis	P value
Glucose at 6 a.m.	134,1 (113,7/154,6)	23,9 (5,7/42,1)	0,010
Glucose at 12 p.m.	144,8 (119,8/169,9)	10,9 (-12,5/34,3)	0,363
Glucose at 5 p.m.	195,7 (159,3/232,1)	-5,8 (-31,5/20,0)	0,659
Glucose at 10 p.m.	153,5 (123,5/183,6)	46,5 (20,3/72,6)	<0,001
Daily average variation	165,5 (141,5/189,5)	14,9 (1,7/28,1)	0,026
Complete daily average variation	142,5 (111,5/173,6)	25,5 (-0,7/51,7)	0,056

The coefficients (left), 95% confidence intervals (within parentheses) and p-values (right) were obtained with PA-GEE regression, taking into account the day of hospitalization as the variable time, the Gaussian family and the identity link function.



**Fig. 1.** Glucose at 6:00- Glucose at 12:00-Glucose at 17:00-Glucose at 22:00 -flexible average glucose-rigid average glucose.

**Table 3**  
Nested multivariate analysis of glucose variation according to the use of corticosteroids in COVID-19 patients.

Associated variables	Glucosa at 6am	Glucose at 10pm	Average glucose
Constant (basal)	92,9 (77,5/108,4) <0,001	105,2 (73,5/136,8) <0,001	113,4 (100,1/126,8) <0,001
Use of corticosteroids	+23,5 (+5,8/+41,2) <0,001	+44,4 (+17,0/+71,7) 0,001	+15,3 (+2,0/+28,7) <0,025
Having diabetes	+81,3 (+53,4/+109,2) <0,001	+118,4 (+87,0/+149,8) <0,001	+101,6 (+70,5/+132,8) <0,001
Obesity	Excluded	-34,9 (-68,8/-1,0) 0,044	Excluded

The coefficients (left), 95% confidence intervals (within parentheses) and p-values (right) were obtained with PA-GEE regression, taking into account day of hospitalization as the variable time, the Gaussian family and the identity link function. Nested models were used in each case (taking into account the p-value as the first step for decision making and the Wald test as the second).

physicians and services of each health institution that is managing patients with diabetes and COVID-19, evaluating their own reality, generating their own management guidelines (based on those that already exist and the results of new research), as well as gradually adapting them.

In the United Kingdom, a meeting of experts on the management of hyperglycemia in patients with diabetes and COVID-19 who receive dexamethasone, promotes the use of insulin therapy schemes with greater insulin requirements and strict glycaemic control. Similar recommendations are suggested by another panel of experts [16,18,19]. However, we still do not have clinical trials to support decision-making [20]. Therefore, it is hoped that future

research will aim to evaluate this situation in controlled populations, with differentiated management with corticosteroids in diabetic and non-diabetic patients suffering from COVID-19 to ratify that these alterations exist on a daily basis, and what would be the best management for this situation, proposing different forms of treatment.

One of our limitations in the study is not having glycated hemoglobin A1c when the patients were admitted, which could unmask undiagnosed diabetes. Another of our limitations in the context of clinical management is the limited number of glucose controls for decision making. In addition, we have limitations of retrospective and non-experimental studies themselves, which do

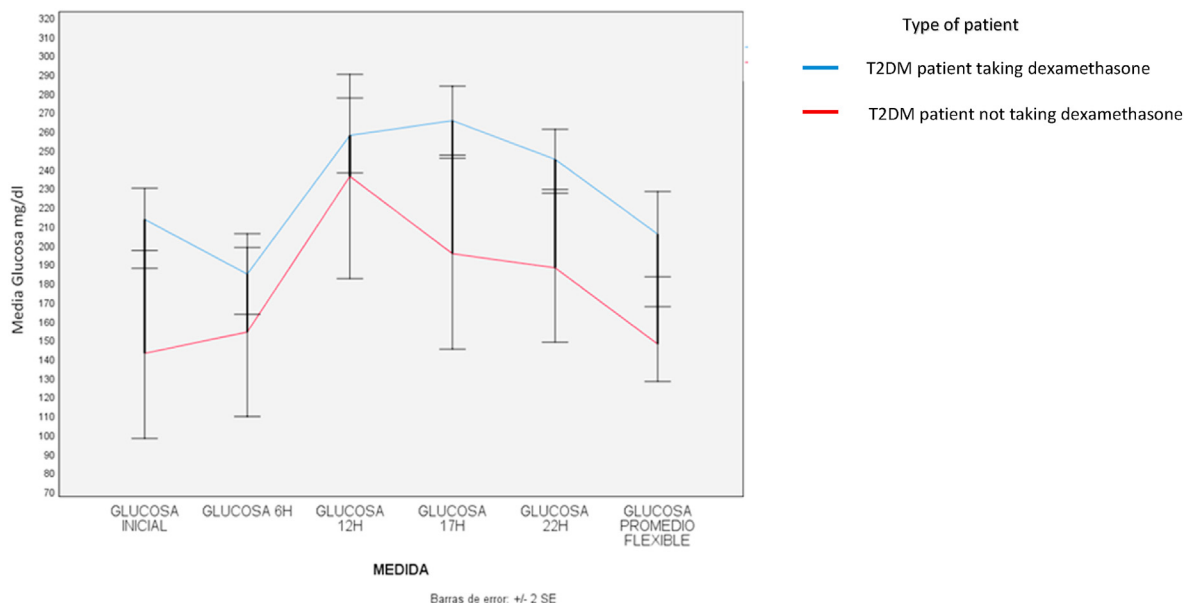


Fig. 2. Initial glucose – Glucose at 6:00 - Glucose at 12:00- Glucose at 17:00- Glucose at 22:00 -flexible average glucose.

not allow us to have all the variables or randomization. Lastly, the dose and timing of administration of corticosteroids has not been taken into account, these are important factors affecting blood glucose values. In spite of all these limitations, the results are extremely important, since they show a major problem in the management of patients with diabetes and COVID-19 (which may currently number over millions worldwide), hence, it is expected that future research will be able to carry out this type of investigation.

Based on the above, it is concluded that those patients who used corticosteroids for the treatment of COVID-19 increased the average glucose per day, especially in the first and last measurement. There was also an increase in these glucose levels in those who had diabetes and those who were obese had a decrease in the last glucose level of the day. In obese patients the reduced glucose values after corticosteroids are unexpected and needs to be demonstrated in futures researches.

**Funding and duality of interest**

The study was self-funded by the authors. F.E. is a medical scientific liaison for SANOFI Peru. The rest of the co-authors report no relevant conflicts of interest related to this work.

**Declaration of competing interest**

The authors declare that there are no conflicts of interest with this article.

**References**

[1] de Salud Ministerio. Análisis Epidemiológico de la Situación Actual de COVID-19 en el Perú, basado en la información de la Vigilancia Epidemiológica y la Investigación de Campo [Internet]. Lima. 2020 [cited 2020 Oct 19]. Available from: <https://www.dge.gob.pe/portal/docs/tools/coronavirus/analisiscoronavirus080520.pdf>.  
 [2] Mejía F MC, Cornejo E, Morello E, Vásquez S, Alave J, et al. Características clínicas y factores asociados a mortalidad en pacientes adultos hospitalizados por COVID-19 en un hospital público de Lima, Perú. [Internet]. SciELO Preprints; [cited 2020 Nov 10]. Available from: <https://doi.org/10.1590/SciELOPreprints.858>.  
 [3] Munayco C, Chowell G, Tariq A, Undurraga EA, Mizumoto K. Risk of death by

age and gender from CoVID-19 in Peru, March-May, 2020. *Aging* 2020 Jul 21;12(14):13869–81.  
 [4] RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med* 2021 Feb 25;384(8):693–704.  
 [5] Meyerowitz EA, Sen P, Schoenfeld SR, Neilan TG, Frigault MJ, Stone JH, et al. Immunomodulation as Treatment for Severe COVID-19: a systematic review of current modalities and future directions. *Clin Infect Dis*. 2021 Jun 15;72(12):e1130–43.  
 [6] Tamez-Pérez HE, Quintanilla-Flores DL, Rodríguez-Gutiérrez R, González-González JG, Tamez-Peña AL. Steroid hyperglycemia: prevalence, early detection and therapeutic recommendations: a narrative review. *World J Diabetes* 2015;6(8):1073–81.  
 [7] Burt MG, Roberts GW, Aguilar-Loza NR, Frith P, Stranks SN. Continuous monitoring of circadian glyceimic patterns in patients receiving prednisolone for COPD. *J Clin Endocrinol Metab* 2011;96(6):1789–96.  
 [8] O’Connell RS, Clinger BN, Donahue EE, Celi FS, Golladay GJ. Dexamethasone and postoperative hyperglycemia in diabetics undergoing elective hip or knee arthroplasty: a case control study in 238 patients. *Patient Saf Surg* 2018;12:30.  
 [9] Nyenwe E, James D, Wan J, Dagogo-Jack S. Glycemic response to oral dexamethasone predicts incident prediabetes in normoglycemic subjects with parental diabetes. *Journal of the Endocrine Society* 2020;4(11):bvaa137.  
 [10] Pasquel FJ, Fayfman M, Umpierrez GE. Debate on insulin vs non-insulin use in the hospital setting-is it time to revise the guidelines for the management of inpatient diabetes? *Curr Diabetes Rep* 2019;19(9):65.  
 [11] Waterer GW, Rello J. Steroids and COVID-19: we need a precision approach, not one size fits all. *Infectious diseases and therapy* 2020:1–5.  
 [12] Alessi J, de Oliveira GB, Schaan BD, Telo GH. Dexamethasone in the era of COVID-19: friend or foe? An essay on the effects of dexamethasone and the potential risks of its inadvertent use in patients with diabetes. *Diabetol Metab Syndrome* 2020;12:80.  
 [13] Ruiz de Adana MS, Colomo N, Maldonado-Araque C, Fontalba MI, Linares F, García-Torres F, et al. Randomized clinical trial of the efficacy and safety of insulin glargine vs. 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(2):158–65.  
 [14] Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *Jama* 2020;324(13):1330–41.  
 [15] Herbst RA, Telford OT, Hunting J, Bullock WM, Manning E, Hong BD, et al. The effects of perioperative dexamethasone on glyceimic control and post-operative outcomes. *Endocr Pract : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 2020;26(2):218–25.  
 [16] Rayman G, Lumb AN, Kennon B, Cottrell C, Nagi D, Page E. Dexamethasone therapy in COVID-19 patients: implications and guidance for the management of blood glucose in people with and without diabetes 2021;38(1):e14378.

- [17] Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, 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(1):16–38.
- [18] Singh AK, Khunti K. Assessment of risk, severity, mortality, glycemic control and antidiabetic agents in patients with diabetes and COVID-19: a narrative review. *Diabetes Res Clin Pract* 2020;165:108266.
- [19] Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *The lancet Diabetes & endocrinology* 2020;8(6):546–50.
- [20] Bloomgarden Z. Does glycemic control affect outcome of COVID-19? *J Diabetes* 2020;12(12):868–9.