VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

Ivona Risovic[1, 2], Danijel Djekic[1], Blazenko Vukovic[1, 2], Vlastimir Vlatkovic [2, 3]

[1]Department of Endocrinology, University Clinical Center of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina
[2]Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia and Herzegovina,
[3]Department of Nephrology, University Clinical Center of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina

Clinical characteristics and managing type 2 diabetes during the COVID-19

ABSTRACT

Background: Diabetes mellitus (DM) is one of the most common comorbidities in people with COVID-19 infection. Inadequate glycemic control is related to high inflammation, hypercoagulability, and mortality in COVID-19 patients. Patients admitted to hospital for COVID-19 might need modifications to their diabetes therapy. The study was aimed at evaluating the association of clinical presentation and glycemic management in patients with type 2 diabetes and COVID-19.

Methods: This retrospective study included 60 patients with type 2 DM and COVID-19, distributed into three groups: group 1 oral agents — 32 patients, group 2 oral agents and basal insulin — 15 patients, group 3 intensive insulin treatment — 13 patients. We measured laboratory parameters, evaluated clinical presentation, and followed glycemic treatment during hospitalization.

Results: Patients on oral antidiabetic drugs had better glycemic control before hospitalization, shorter duration of DM, and normal weight according to BMI compared with the other two groups. The most common symptoms of COVID -19 were: fever, cough, and fatigue. For better glycemic control we added basal insulin in 15 patients in group 1 (50%) and 9 patients need intensive insulin treatment in group 2 (60%). We discounted metformin in two patients in group 1 and three patients in group 2. A total of 7 patients died (11.6 %) during hospitalization, including 3 deaths in group 2 (5%), and 4 deaths in group 3 (6.6%).

Conclusions: Poorer glycemic control before COVID -19 is associated with higher inflammation parameters, worse outcomes, and required modification of their treatment during hospitalization. (Clin Diabetol 2022, 11; 1: 20–25)

Keywords: COVID-19, type 2 diabetes mellitus, glycemic control, management

Introduction

In December 2019, coronavirus disease 2019 (COVID-19), caused by the new highly infectious organism now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China. Following the rapid spread of COVID -19, World Health Organization declared COVID-19 a global pandemic in March, 2020 [1]. On 24 May 2021, 166 860 081 globally confirmed cases and 3 459 996 confirmed deaths of COVID -19 have been reported on the World Health Organization COVID-19 dashboard [2]. On 24 May 2021, 63 831 confirmed cases of COVID -19 have been reported on the Public Health Institute of the Republic of Srpska [3].

Diabetes mellitus (DM) is one of the most common comorbidities seen in people with COVID-19, second only to hypertension [4]. COVID-19 has a highly variable clinical presentation, ranging from asymptomatic to severe respiratory symptoms and death. People with type 2 diabetes are known to not only be more susceptible to infections in general but also require hospitalization more often, resulting in an overall worse prognosis [5].

People with diabetes who have not yet been infected with the SARS-CoV-2 virus should intensify their metabolic control as needed as means of primary

Address for correspondence:
Ivona Risovic
12 babies nn, 78000 Banja Luka
Bosnia and Herzegovina
e-mail: ivona.risovic@gmail.com
Clinical Diabetology 2022, 11; 1: 20–25
DOI: 10.5603/DK.a2022.0010
Received: 30.07.2021 Accepted: 24.10.2021

prevention of COVID-19 disease [6]. All patients with COVID-19 disease and diabetes require continuous and reliable glycemic control [7]. Inadequate glycemic control is related to high inflammation, hypercoagulability, and mortality in COVID-19 patients. The ideal antidiabetic drug used in DM patients with coexisting COVID-19 infection should not only lower blood glucose but should also not worsen the prognosis of COVID-19 infection [7, 8]. Glucose lowering medications commonly used to treat DM might have effects on COVID-19 pathogenesis, and these effects could have implications for the management of patients with DM and COVID-19 [9]. In the presence of mild COVID-19 in an out-patient setting, usual glucose-lowering therapies for patients with diabetes could be continued if the patients eat and drink adequately and a more frequent blood glucose monitoring regimen is implemented. Patients admitted to hospital for severe COVID-19 might need modifications to their diabetes therapy, including withdrawing ongoing treatments and initiating insulin therapy. Such a decision should be based on the severity of COVID-19, nutritional status, actual glycemic control, risk of hypoglycemia, renal function, and drug interactions [10–13].

We performed a retrospective study to evaluate the association between clinical presentation and management in type 2 DM patients on different antidiabetic drugs and COVID-19.

Methods

A total of 60 patients with type 2 DM at Internal Clinic for COVID-19 in University Clinical Center of the Republic of Srpska, Banja Luka from March 1 to May 17, 2021 were retrospectively reviewed. Inclusion criteria were: confirmed COVID-19 infection as determined by a positive reverse transcriptase-polymerase chain reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab, personal history of diabetes. All patients had moderate COVID-19 disease with fever, respiratory tract symptoms, and pneumonia on imaging without the need for invasive ventilation. All the subjects have given informed consent to participate in the research. The study was carried out according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee.

The laboratory, symptoms and signs, medical history, were obtained from the electronic medical record. Collected data included clinical characteristics prior to hospitalization including complications, comorbidities, and routine treatments. The COVID-19 patients were divided into three groups according to antidiabetic drugs before hospitalization: group 1 oral agents — 32 patients, group 2 oral agents and basal insulin —15 patients, group 3 intensive insulin treatment — 13 patients. In group 1: 6 patients had only metformin, 26 had metformin plus sulfonylureas, 4 had metformin plus DPP-4 inhibitors. In group 2: 7 patients had combinations: metformin plus glargine 100, 4 had metformin and glargine 300, 4 had metformin and degludec. The following parameters were recorded: blood leukocyte, lymphocyte, and granulocyte count values, glucose, C-reactive protein (CRP), ferritin, fibrinogen, lactate dehydrogenase (LDH) levels, D-dimer, urea, creatinine.

Statistical analyses

The descriptive statistics for quantitative data were expressed as mean and standard deviation, and qualitative data was expressed as proportions. To compare means between continuous variables with normal distribution, we used the Student's t-test for unpaired samples, or an ANOVA test for multiple unpaired samples was used (if the observed features have a normal distribution), and a nonparametric Mann-Whitney test for two unpaired samples or non-parametric Kruskal -Wallis test for multiple unpaired samples (if the observed features do not have a normal distribution). A p-value < 0.05 was considered statistically significant. Analyses were performed using the IBM SPSS Statistics 21.0 (IBM Corp, Armonk, NY).

Results

We included 60 patients, 36 men and 24 women. The median age was 71 years, ranging from 42 to 86 years. All patients had hypertension as comorbidity, followed by cardiovascular or cerebrovascular disease (18%), and chronic kidney disease (6%). Three patients (5%) had chronic renal failure undergoing long-term maintenance hemodialysis. Four patients had cancer (6%). Saturation O2 was 95% in group 1, 90% in group 2, and 92 % in group 3 without oxygen inhalation at the time of admission. A total of 7 patients died (11.6 %) during hospitalization, including 3 deaths in group 2 (5%), and 4 deaths in group 3 (6.6%). The baseline characteristics of the study population are shown in Table 1. Laboratory parameters are shown in Table 2. The average glycemic level during hospitalization showed at Figure 1.

The most symptoms of COVID -19 infection were: fever, cough, and fatigue.

All patients received corticosteroids drug during hospitalization. For better glycemic control we added basal insulin in 15 patients in group 1 (50%), 9 patients need intensive insulin treatment in group 2 during hospitalization (60%). We discounted metformin in two patients in group 1 and three patients in group 2. The sulfonylureas drugs were discounted before insulin treatment.

Table 1. Baseline characteristics of the study population

	All patients (n, %)	Group 1	Group 2	Group 3	P
Age [years]	71.3 ± 3.43	66.3 ± 5.5	70.12 ± 3.3	77.5 ± 1.5	p < 0.001
Gender (males/females)	36/24	24/14	6/4	6/6	
Diabetes [years]	7.5 ± 1.23	5.14 ± 0.8	7.56 ± 1.3	9.8 ± 1.6	p < 0.001
Signs and symptoms					
Fever, %	58 (96)	30 (83)	8 (80)	10 (83)	ns
Cough	45 (75)	28 (77)	8 (80)	9 (75)	ns
Fatigue	52 (86)	25 (69)	6 (60)	8 (66)	ns
Diarrhea	33 (55)	20 (55)	5 (50)	6 (50)	ns
Myalgia	25 (41)	18 (30)	3 (30)	4 (33)	ns
Shortness of breath	15 (25)	12 (33)	2 (20)	4 (33)	p < 0.05
Time of symptoms before	6.54 ± 1.98	6.53 ± 2.16	6.45 ± 3.1	6.65 ± 0.7	ns
Hospitalization [days]	14.79 ± 5.09	14.52 ± 7.51	15.01 ± 4.2	14.85 ± 3.56	ns

ns — non-significant

Table 2. Laboratory parameters of study patients

	All patients	Group 1	Group 2	Group 3	P
White blood cells [× 10^9/L]	8.15 ± 1.5	8.07 ± 1.5	8.3 ± 0.9	8.1 ± 2.0	ns
Granulocytes [× 10^9/L]	5.26 ± 1.59	5.2 ± 2.0	5.2 ± 1.2	5.4 ± 1.07	ns
Lymphocytes [× 10^9/L]	0.80 ± 0.19	0.88 ± 0.21	0.79 ± 0.13	0.74 ± 0.25	ns
CRP [mmol/L]	110 ± 18.96	105 ± 12.53	98 ± 12.36	128 ± 32	p < 0.001
Ferritin [μg/L]	687 ± 189	651 ± 212	698 ± 231	712 ± 124	p < 0.05
D-dimer [ng/mL]	2.31 ± 0.82	1.54 ± 0.23	2.56 ± 1.02	2.85 ± 1.23	p < 0.001
HbA1c [%]	7.93 ± 1.28	7.4 ± 1.25	8.1 ± 0.50	8.3 ± 2.1	p < 0.05
Glycemia [mmol/L]	8.15 ± 1.02	7.54 ± 0.78	8.15 ± 1.03	8.78 ± 1.25	p < 0.05
LDH [U/L]	292 ± 154.07	251 ± 152.23	305 ± 186	322 ± 124	p < 0.05
BMI [kg/m^2]	25.65 ± 4.30	24.12 ± 7.3	25.68 ± 2.1	26.14 ± 3.51	p < 0.05

BMI — body mass index; CRP — C-reactive protein; HbA1c — glycated hemoglobin; LDH — low density proteins; ns — non significant

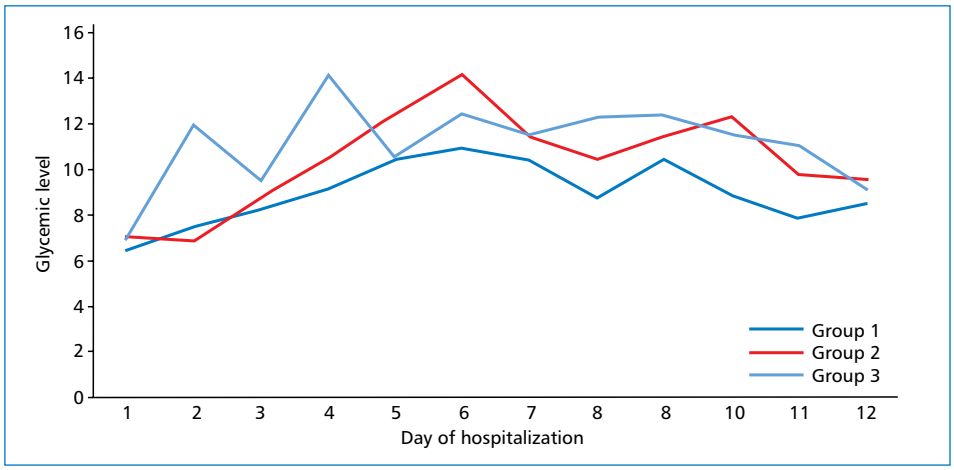

Figure 1. The average glycemic level in groups 1, 2 ,3 during hospitalization

Discussion

One of the principal comorbidities of patients with COVID-19 is type 2 diabetes, resulting as an independent predictor for worse outcomes. Type 2 diabetes mellitus as a consequence of metabolic syndrome and obesity predisposes to immune dysfunction with raised inflammatory factors and chemokines. Maintaining good glycemic control is mandatory [14].

In our study, patients on oral antidiabetic drugs had better glycemic control before hospitalization, shorter duration of DM, and normal weight according to BMI. Patients on intensive insulin treatment were the oldest, had a longer duration of diabetes and poorer glycemic control compared with the other two groups. Patients group 2 and 3 group were overweight. We did not find any difference in clinical presentation between groups. The three most common symptoms were: fever, cough, and fatigue. Other authors also showed that these symptoms were more frequent in their study. Some authors had found differences in clinical presentation COVID -19 when compared to uncontrolled and controlled type 2 diabetic patients. Bhandari et al. had shown that clinical presentation was more pronounced in the uncontrolled diabetes group as compared with the controlled diabetes group [15].

Diabetes mellitus is associated with the pro-inflammatory state and the attenuation of the innate immune response [16]. Metabolic disorders may impair the functions of macrophages and lymphocytes and thereby lead to low immune function, which predisposes people to disease complications [17]. Excessively raised ferritin level is an indicator of activation of the monocyte-macrophage system that contributes significantly to the inflammatory storm associated with COVID-19. When we analyzed inflammatory parameters our results showed that patients groups 2 and 3 with the poorer glycemic control had higher average total leukocyte, CRP, ferritin, and relative lymphocytopenia. Other studies showed that inflammatory responses were higher in diabetic patients especially in uncontrolled type 2 diabetic patients. Inflammation-associated hypoxia might induce thrombin activation with a consequent unfolding of the exogenous coagulation pathway. Inflammatory storm in COVID-19 is associated with a significant rise in D-dimer levels [17, 18]. Our results showed that levels of D-dimer difference between group and patients with poorer glycemic control had significantly increased levels of D-dimer as compared with better controlled diabetic patients. This finding is an indication of a hypercoagulable state and the possibility of developing complications of COVID-19 as pulmonary thromboembolism. For these reasons, these patients need intensive monitoring [7, 16, 17].

We did not find any significant difference between our groups in the average duration of hospital stays. Other authors have shown significantly prolonged hospitalization stays in patients with uncontrolled diabetes as compared with patients with controlled diabetes [15].

Deaths were more common in group 3. Probably older age, longer duration of diabetes, and higher HbA1c before hospitalization were risk factors for worse outcomes in these groups. Diabetes is a bad prognostic factor for outcome in COVID-19 [15]. Recent research showed that diabetes is associated with a worse prognosis and these patients had higher mortality rates [4, 6, 19].

In a patient with diabetes and a confirmed COVID-19 infection, strict blood glucose monitoring is required [11, 20]. Infections are known to result in less well-controlled diabetes [19]. A recent study pointed out that the increased baseline glycemic level was significantly associated with a higher rate of developing ARDS in patients with COVID-19. The study by Zhu et al. showed that well-controlled blood glucose (glycemic variability within 3.9 to 10.0 mmol/L) was associated with significantly lower mortality compared to patients with poorly controlled blood glucose (upper limit of glycemic variability exceeding 10.0 mmol/L) during hospitalization. These results provide clinical evidence linking improved glycemic control to better outcomes in COVID-19 patients who have preexisting type 2 diabetes [21]. Several expert recommendations and reviews have discussed in detail glycemic management in patients with COVID-19 [8]. Although metformin-induced lactic acidosis and SGLT2i-related diabetic ketoacidosis are rare events, these drugs are not recommended to be continued for patients with severe COVID-19 in order to reduce the risk of acute metabolic decompensation [11]. In addition, sulfonylureas are best avoided in hospitalized patients with severe illness due to the increased risk of hypoglycemia [22]. Importantly, for mild COVID-19 patients with diabetes or diabetic outpatients without any symptoms of infection, prophylactically discontinuing these drugs is not recommended. As for DPP-4 inhibitors and GLP-1receptor agonists, currently, there is no adequate evidence to suggest that these agents should be discontinued [21, 22]. Of note, if drugs are discontinued or need better glycemic control, the alternative treatment option should be insulin [11]. Insulin associated with constant glucose monitoring is the first-choice treatment for hyperglycemia in hospital settings. An intensive regimen with basal and prandial insulin analogs is the best treatment for non-critically ill hospitalized patients with good or poor nutritional oral intake, in order to reach the recommended target

glucose range of 7.8–10 mmol/L. In patients who receive basal insulin, fast-acting insulin is used for acute hyperglycemia correction; blood glucose fluctuation during insulin therapy prerequisites strict and frequent monitoring [12, 14, 22, 23].

We did not discontinue oral antidiabetic drugs when they start hospitalization. We followed up individually with each patient a made therapeutic plan by blood glucose, clinical presentation, the severity of COVID-19, and comorbidity. For the severe clinical presentation, we temporarily discontinued metformin in a few patients in groups 1 and 2.

Recent clinical studies have provided supportive evidence for the use of glucocorticoids in patients with COVID-19. Hence, treatment with glucocorticoids is likely to pose great challenges for glycemic control in COVID-19 patients with preexisting diabetes [11, 23–25]. All our patients received corticosteroids drug during hospitalization. When we used corticosteroid drugs in the treatment of COVID-19 half of patients from group 1 need for insulin treatment. In group 2 more than half of patients need intensive insulin treatments. We discontinued sulfonylurea when added insulin. Previous studies also confirmed that half of insulin naïve patients need insulin treatment during COVID-19 infection and intensive treatment in patients who already used insulin [22, 23]. Sardu et al. showed that in a cohort of 59 patients, 26 of whom had previously diagnosed diabetes, those given intravenous insulin had a more positive outcome than those who were not [23]. However, Chen et al found that COVID-19 patients taking insulin, although they presented with significantly different inflammatory markers (higher CRP, procalcitonin, and erythrocyte sedimentation rate), they did not have an overall difference in severity than to patients not taking insulin [19]. For COVID-19 patients comorbid with diabetes, the optimal goal of glucose control and tailored therapeutic strategy should be formulated based on age, coexisting comorbidities, clinical classification, and other risk factors [14, 20, 21].

Conclusions

Diabetic control before COVID-19 is associated with severity, outcome and has influence on glycemic management in COVID-19. Glycemic management in COVID-19 with preexisting type 2 diabetes should be individualized. Insulin therapy is a basic option for glycemic regulation in these patients.

Conflicts of interest

None declared.

REFERENCES

1. Zhu Na, Zhang D, Wang W, et al. China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382(8): 727–733, doi: 10.1056/NEJMoa2001017, indexed in Pubmed: 31978945.
2. World Health Organization. Weekly operational update on COVID-19 - 24 May 2021. https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---24-may-2021 (26.05.2021).
3. Public Health Institute of Republic of Srpska. Epidemiology data in Republic of Srpska. https://www.phi.rs.ba/index.php?view=clanak&id=1779 (25.05.2021).
4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229): 1054–1062, doi: 10.1016/S0140-6736(20)30566-3, indexed in Pubmed: 32171076.
5. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care. 2003; 26(2): 510–513, doi: 10.2337/diacare.26.2.510, indexed in Pubmed: 12547890.
6. Hill MA, Mantzoros C, Sowers JR. Commentary: COVID-19 in patients with diabetes. Metabolism. 2020; 107: 154217, doi: 10.1016/j.metabol.2020.154217, indexed in Pubmed: 32220611.
7. 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, doi: 10.1016/j.diabres.2020.108266, indexed in Pubmed: 32533989.
8. Li G, Chen Ze, Lv Z, et al. Diabetes mellitus and COVID-19: associations and possible mechanisms. Int J Endocrinol. 2021; 2021: 7394378, doi: 10.1155/2021/7394378, indexed in Pubmed: 33859687.
9. Lim S, Bae JH, Kwon HS, et al. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol. 2021; 17(1): 11–30, doi: 10.1038/s41574-020-00435-4, indexed in Pubmed: 33188364.
10. Corrao S, Pinelli K, Vacca M, et al. Type 2 Diabetes Mellitus and COVID-19: A Narrative Review. Front Endocrinol (Lausanne). 2021; 12: 609470, doi: 10.3389/fendo.2021.609470, indexed in Pubmed: 33868163.
11. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020; 8(6): 546–550, doi: 10.1016/S2213-8587(20)30152-2, indexed in Pubmed: 32334646.
12. Lalau JD, Al-Salameh A. Management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020; 8(8): 666–667, doi: 10.1016/S2213-8587(20)30231-X, indexed in Pubmed: 32707108.
13. Papadokostaki E, Tentolouris N, Liberopoulos E. COVID-19 and diabetes: What does the clinician need to know? Prim Care Diabetes. 2020; 14(5): 558–563, doi: 10.1016/j.pcd.2020.06.010, indexed in Pubmed: 32654982.
14. Longo M, Caruso P, Maiorino MI, et al. Treating type 2 diabetes in COVID-19 patients: the potential benefits of injective therapies. Cardiovasc Diabetol. 2020; 19(1): 115, doi: 10.1186/s12933-020-01090-9, indexed in Pubmed: 32698837.
15. Bhandari S, Rankawat G, Singh A, et al. Impact of glycemic control in diabetes mellitus on management of COVID-19 infection. Int J Diabetes Dev Ctries. 2020 [Epub ahead of print]: 1–6, doi: 10.1007/s13410-020-00868-7, indexed in Pubmed: 32905072.
16. Yang J, Zheng Ya, Gou Xi, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020; 94: 91–95, doi: 10.1016/j.ijid.2020.03.017, indexed in Pubmed: 32173574.

17. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020 [Epub ahead of print]: e3319, doi: 10.1002/dmrr.3319, indexed in Pubmed: 32233013.
18. Costa VO, Nicolini EM, da Costa BMA, et al. Evaluation of the risk of clinical deterioration among inpatients with COVID-19. Adv Virol. 2021; 2021: 6689669, doi: 10.1155/2021/6689669, indexed in Pubmed: 34257657.
19. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223): 507–513, doi: 10.1016/S0140-6736(20)30211-7, indexed in Pubmed: 32007143.
20. Doupis J, Avramidis K. Managing diabetes during the COVID-19 pandemic. Eur Endocrinol. 2020; 16(2): 85–87, doi: 10.17925/EE.2020.16.2.85, indexed in Pubmed: 33117436.
21. Zhu L, She ZG, Cheng Xu, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020; 31(6): 1068–1077.e3, doi: 10.1016/j.cmet.2020.04.021, indexed in Pubmed: 32369736.
22. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev. 2020; 41(3), doi: 10.1210/endrev/bnaa011, indexed in Pubmed: 32294179.
23. Sardu C, D'Onofrio N, Balestrieri ML, et al. Outcomes in patients with hyperglycemia affected by Covid-19: Can we do more on glycemic control? Yearbook of Paediatric Endocrinology. 2020; 43(7): 1408–1415, doi: 10.2337/dc20-0723, indexed in Pubmed: 32430456.
24. 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(1): e14378, doi: 10.1111/dme.14378, indexed in Pubmed: 32740972.
25. 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(10): 2154, doi: 10.3390/jcm10102154, indexed in Pubmed: 34065762.