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THE EFFECT OF METHYLPREDNISOLONE VERSUS DEXAMETHASONE IN INCREASING THE DIABETOGENIC EFFECT OF SARS-CoV-2 INFECTION AND THE DEVELOPMENT OF A NEW-ONSET DIABETES MELLITUS

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Abstract:

SARS-CoV-2 causes predominantly lung disease, but by way of binding to the angiotensin-converting enzyme 2 (ACE2) receptors, it can attack key metabolic organs and may lead to alterations of glucose metabolism.

The aim of the study was to examine the effect of methylprednisolone compared with dexamethasone on the glycaemic control as well as the development of new-onset diabetes in patients who were hospitalized due toCOVID-19 pneumonia.

We reviewed the records of 203 consecutive patients who were hospitalized with a clinical presentation of COVID-19 pneumonia in the modular hospital at the University Clinic for Infectious Diseases and Febrile Conditions in Skopje, from December 2020until May 2021.

We identified 65 patients with diabetes (32,0%), 49 patients (75%) of whichwith pre-existing diabetes, and 16 (25%) with newly diagnosed diabetes.

Impaired glycoregulation was recorded in 19,2% of patients, of whom 5,5% did not receive any corticosteroid-therapy, 22,4% were treated with methylprednisolone – pulse doses,and 21,4% were treated with dexamethasone. Patients with diabetes had a 1,9 times (CI 0,9-3,9) higher mortality rate than non-diabetic patients.

We suggest that, if corticosteroid therapy is necessary during the treatment of COVID-19 pneumonia, it is safer to administer dexamethasone than methylprednisolone, especially in patients who have pre-existingdiabetes or are at risk ofdeveloping diabetes.

Deterioration of glycoregulation and the need to replace oral antidiabetic therapy with insulin are common. New-onset diabetes often persists even after recovering from Covid-19.

***Keywords*:** SARS-CoV-2, Covid-19, pneumonia, corticosteroid therapy, glycoregulation, diabetes mellitus.

Introduction

SARS-CoV-2 infection was thought to be predominantly lung disease, pneumonia progressing to acute respiratory distress syndrome, but depending on the viral load, through angiotensin-converting enzyme 2 (ACE2) receptors it can attacks other organs, such as heart, liver, kidney, brain, endothelium, pancreatic beta cells, adipose tissue, the small intestine, immune cell, and RBC [1].

Thus, it can be assumed that SARS-CoV-2 may cause alterations of glucose metabolism, along with well-recognized stress response to severe disease.

The systemic inflammatory response can be decreased or inhibited by the use of corticosteroids. Routine use of corticosteroid therapy is not recommended in the treatment of SARS-CoV-2 infection. Data for and against corticosteroid use can be found in the literature, improvement and deterioration of the clinical outcome are referred (mostly prednisone or methylprednisolone) in patients with pulmonary infections.

In pneumonia caused by influenza viruses, corticosteroid therapy induces worse clinical presentation, mainly by provoking secondary bacterial infection [2].

Use of corticosteroids for COVID-19 hospitalized patients is largely based on recommendations emerging from data of the RECOVERY trial [3].

Lower mortality was reported in patients treated 10 days with dexamethasone versus patients who received standard of care [3].

The use of corticosteroids reduces the anti-inflammatory response to infection, reduces the need for oxygen and the need for ICU. However, methylprednisolone and dexamethasone do not prevent the negative effects and complications of the virus (avascular necrosis, psychosis, diabetes, delayed viral clearance) [4-6].

Therapy with glucocorticoids exacerbate hyperglycaemia in people with diabetes and may precipitate hyperglycaemia and new-onset diabetes in those without diabetes [7].

There is an increasing number of studies linking corticosteroid therapy to the onset of new diabetes, but no study has provided an explanation for this.

The primary aim of this study was to compare the effect of diabetes on clinical outcome of hospitalized patients with COVID-19 pneumonia and the secondary aim was to examine the effect of methylprednisolone compared to dexamethasone on the new onset of diabetes in the same patient population.

Methods

1.1 Study design

This is a retrospective observational study of 203 consecutive patients with Covid-19 pneumonia admitted to the modular hospital at the University Clinic for Infectious Diseases and Febrile Conditions in Skopje, from December 2020 until May 2021.

All patients had a positive SARS-CoV-2 PCR test result at admission as well as radiographically confirmed pneumonia. Patients under 18 years of age were excluded.

As per hospital protocol, all patients were treated with intravenous ceftriaxone (1g b.i.d. for 7 days) plus azithromycin (500 mg o.d. for 5 days) or clarithromycin (500 mg b.i.d. for 7 days).

Clinical parameters were measured daily by the hospital clinical staff from day 1 until discharge or death. Other laboratory tests were performed as indicated.

Corticosteroid therapy during the examined period was allowed in the hospital protocol.

Different corticosteroids were used at the discretion of the responsible physician. Two different regiments of corticosteroid therapy were as followed: a) Methylprednisolone - 240 mg once daily for three days, lowered to 80 mg twice daily for the next three days, than 40 mg twice daily for three days, and 20 mg daily the following days depending on clinical presentation; and Dexamethasone - 6 mg daily for 10 days.

Pre-existing diabetes was defined based on history, prior electronic medical records reporting a diagnosis of diabetes, or ongoing therapy with glucose-lowering medications. Newly diagnosed diabetes was defined by a HbA1c value > 6.5%; or measured fasting glycaemia above 7,5 mmol/l or random measured glycaemia above 11,1 mmol/l in non-diabetic patient (re-evaluation of elevated glycaemia via electronic health card).

Worsening of glycaemic control was defined in diabetic patients who have fasting glycaemic levels above 11,1 mmol/l despite oral antidiabetic therapy and in patients who were switched from oral to insulin therapy during hospitalization.

Patients were divided and comparatively analysed in two groups based on diabetic status.

One group – non- diabetic patients, and other group- diabetic patients that included patients with known, and new-onset diabetes.

For all patients, the following information were recorded: demographics (age, sex), comorbidities (cardiovascular disease, chronic obstructive pulmonary disease, asthma, hypo/hyperthyroidism), cardiovascular risk factors (obesity, dyslipidaemia, arterial hypertension, smoking history), ongoing therapies during hospitalization, blood tests during hospitalization, biomarkers indicating inflammation.

1.2 Statistical analysis

IBM SPSS statistical program (version 22) was used for statistical analysis. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables as numbers and/or percentages.

Comparative statistics was performed with Student t-test for continuous variables and chi-Square test for categorical variables. Odds Ratios were calculated and Cochran's and Mantel-Haenszel statistics was performed for estimation of statistical significance of OR.

Univariate logistic regression analysis was performed to identify variables significantly associated with the outcome of interest, and multivariate regression analysis to identify independent outcome predictors. Mann – Witney test was used to test differences in mortality rate between different patient characteristics. Significance was determined at the level of < 0,05.

Results

1.1 Patient characteristics

We collected data from 203 adult patients, mean age was 63,3 ± 13,2 (22-99 years), 58,6% were male and 41,4% female. We identified 65 patients with diabetes (32,0%), 49 (75%) of whom with known, and 16 (25%) patients with newly diagnosed diabetes.

As compared to individuals without diabetes, those with diabetes were older, had a higher prevalence of hypertension, coronary artery disease, hyperlipidaemia, and hypothyroidism. Patient characteristics are outlined in **table 1**.

Table 1. Characteristics of COVID-19 patients according to diabetes status on admission.

	All patients	**No diabetes**	**Diabetes + NDD**	**p-value**	**Odds ratio (CI)**
All patients	203 (100%)	138 (68%)	65 (32%)	ns	
Gender • males • females	 119(58,6%) 84(41,4%)	 84(60,9%) 54(39,1%)	 35(53,8%) 30(46,2%)	ns	OR 1,3 (0,7-2,4) for females
Age	63,2 ± 13,2	61,6 ± 13,9	66,7 ± 10,1	0,006	
Hypertension	62,1 %	52,9%	81,5%	0,000	OR 3,9 (1,9-8,0)
Hyperlipidemia	13,8%	6,4%	23,1%	0,009	OR 2,8 (1,3-6,5)
Obesitas (BMI >30)	24,1%	23,2%	26,2%	ns	
Asthma	3,4 %	2,6%	6,1%	ns	
COPD	8,8%	9,1%	6,1%	ns	
Hypothyroidism	6,4%	5,1%	9,2%	ns	OR 1,9 (0,6-5,9)
Atrial fibrillation	8,4%	8,0%	9,2%	ns	
Heart failure	6.9%	8,0%	4,6%	ns	
CAD	7,4%	4,3%	13,8%	0,019	OR 3,5 (1,2-10,4)
CRP	157,8 ± 115,7	61,2±115,4	150,4 ± 117,8	ns	
LDH (U/I)	570,8 ± 378,6	559,3 ± 392,4	596,3 ± 333,5	ns	
BUN (mmol/l)	9,7 ±7,8	8,8 ±7,9	11,6 ±7,0	0,014	
Creatinine (μmol/l)	97,6 ± 89,8	91,5 ± 72,0	110,5 ± 114,6	ns	
D-dimer (ng/ml)	3188,3 ± 5385,6	3256,5±5996,1	3039,7±2236,5	ns	
Haemoglobin (g/l)	121,1 ± 20,7	121,3 ± 19,7	119,0 ± 23,6	ns	
WBC (10^9/L)	12,5 ± 5,7	12,2 ± 5,9	13,1 ± 4,9	ns	
Platelets (10^9/L)	238,9 ± 114,1	249,4 ± 124,0	216,6 ± 84,0	0,040	
AST (U/l)	93,9 ± 109,6	103,9 ± 119,8	71,6 ± 61,5	0,016	
ALT (U/l)	125,2 ± 131,0	131,6 ± 118,2	110,2 ± 153,4	ns	
Mortality	43 (21,2%)	24 (17,4%)	19 (29,2%)	0,043	OR 1,9 (1,0-3,9)

Data presented as mean (SD) or as percentage.

(BMI -body mass index; COPD- chronic obstructive pulmonary disease; CAD- coronary artery disease; CRP- C-reactive protein; LDH - lactat dehydrogenase; BUN – blood urea nitrogen; WBC- white blood cells; AST - aspartat aminotransferase; ALT- alanin aminotransferase)

Symptoms at admission in diabetic and non-diabetic patients were similar. As for hemogram and biochemical variables diabetic patients had higher values of BUN, lower values of platelets and AST. Other laboratory findings showed no significant differences. In-hospital pharmacological treatment was similar in subjects with or without diabetes.

Patients with diabetes have 1,9 times (CI 0,9-3,9) higher mortality rate than non-diabetic patients.

1.1. Corticosteroid therapy and diabetic status

Due to the mild clinical presentation 36 patients (17,7%) did not receive corticosteroid therapy, 125 patients (61.6 %) were treated with methylprednisolone -pulse doses with gradual reduction, and 32 patients (15,7%) were treated with dexamethasone.

Forty-nine patients had been diagnosed with diabetes prior to hospitalization with COVID-pneumonia. During hospitalization 16 patients were diagnosed with diabetes- newly diagnosis, and 23 patients (47% of diabetic patients) had deterioration of glycemic control. None of the newly diagnosed diabetic patients had prior medical records of high blood glucose levels or familial relevant anamnestic data.

Impaired glycoregulation was recorded in 19,2% of patients, out of which 5.5% did not receive corticosteroid-therapy at all, 22,4% were treated with methylprednisolone – pulse doses, and 21,4% were treated with dexamethasone. Deterioration of glycoregulation in patients with diabetes has been recorded in 23 patients, and 16 patients developed diabetes.

No statistically significant difference was reached depending on type of corticosteroid therapy, but tendency toward worse results in those treated with methylprednisolone was evident. **(Figure 1, Table 2)**

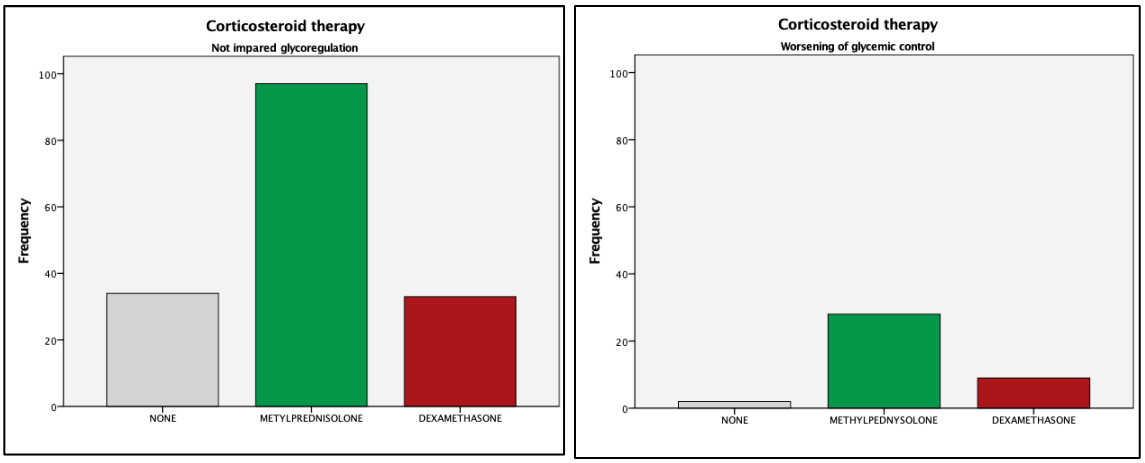

Figure 1. Corticosteroid therapy in patient who did not and who developed worsening of glycaemic control. (OAD-oral antidiabetic drugs)

Table 2. Effect of corticosteroid therapy on worsening of glycemic control.

variable	Total (203pts)	No corticosteroid therapy (36pts)	Methylprednisolone (125pts)	Dexamethasone (42pts)	p-value
Impaired glycoregulation	39 (19,2%)	2 (5,5%)	28 (22,4%)	9 (21,4%)	0,071
From OAD to Insulin	23 (11,3%)	1 (2,8%)	15 (12,0%)	7 (9,5%)	0,026
Newly developed diabetes	16 (7,9%)	1 (2,8%)	13 (10,4%)	2 (4,8%)	ns

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	NONE			4,424	2	,109			
	Metylprednisolone	1,591	,759	4,397	1	,036	4,907	1,110	21,704
	Dexamethasone	1,534	,819	3,508	1	,061	4,636	,931	23,086
	Constant	-2,833)	,728	15,162	1	,000	,059		

a. Variable(s) entered on step 1: Corticosteroid therapy

Two months after discharge from the hospital we reviewed the medical records of patients with new-onset diabetes and 5 of the patients were still on oral antidiabetics, one was still on insulin therapy, and for the others we didn't find any electronic documentation.

1.2. Mortality data

The main outcome of interest was in-hospital mortality. Forty-three patients (21,2%) died during hospitalisation. Factors affecting a fatal outcome were age, admission oxygen saturation, presence of arterial hypertension and chronic obstructive pulmonary disease. **(Table 3)**

Table 3. Characteristics of COVID-19 patients according to fatal outcome

Parameter	Alive	Dead	p-value
Age	61,47	69,84	<0,03*
Male gender	60,6%	51,2%	0,265
O2 saturation on admission 93-100% 85-92% 70-85% <70%	 39,4% 36,3% 18,8% 5,6%	 14,0% 23,3% 37,2% 25,6%	 <0,03*
Presence of COPD	5,6%	18,6%	<0,03*
Presence of Asthma	3,8%	2,3%	0,650
Presence of hypothyroidism	5,6%	9,3%	0,383
Presence of hypertension	58,1%	74,4%	0.034*
Cardiomyopathy	6,3%	9,3%	0,484
Hyperlipidemia	12,5%	18,6%	0,304
Diabetes mellitus on admission	21,9%	32,6%	0,147
Obesitas (BMI>30)	24,4%	23,3%	0,879
Worsening of glycoregulation (in diabetic and non-diabetic patients)	16,3%	30,2%	0,039*

All variables that demonstrated significant association with fatal in-hospital outcome, were subjected to multivariate binary logistic regression analysis. In a model with Chi square 42,622, p<0,000, at the last step three independent predictors were identified: advanced age, O2 saturation at admission and presence of COPD. **(Table 4)**

Table 4. Multivariate binary logistic regression analysis showing independent predictors for fatal outcome.

							95% C.I.for EXP(B)	
		B	S.E.	Wald	Sig.	Exp(B)	Lower	Upper
Step 1[a]	Age	.050	.020	6.040	.014	1.051	1.010	1.094
	Gender	.379	.404	.880	.348	1.460	.662	3.221
	O2-saturation	.805	.208	14.976	.000	2.236	1.488	3.361
	COPD	1.534	.631	5.907	.015	4.638	1.346	15.984
	Asthma	-.913	1.167	.612	.434	.401	.041	3.950
	Hypothyroidism	.130	.734	.031	.860	1.138	.270	4.802
	Hypertension	.310	.463	.447	.504	1.363	.550	3.376
	Cardiomyopathy	-.156	.716	.047	.828	.856	.210	3.482

	Overwight (BMI>30)	-.065	.473	.019	.891	.937	.371	2.370
	Newly diagnosed diabetes	-.146	.786	.035	.852	.864	.185	4.028
	Impared glucoregulation	.527	.558	.892	.345	1.693	.568	5.051
	Constant	-6.706	1.551	18.705	.000	.001		
Step 9[a]	Age	.054	.019	7.968	.005	1.056	1.017	1.096
	O2-saturation	.810	.202	16.100	.000	2.249	1.514	3.340
	COPD	1.347	.588	5.257	.022	3.846	1.216	12.165
	Constant	-6.121	1.364	20.123	.000	.002		

Discussion

COVID-19 infection has resulted in striking changes in patients' metabolism with significant elevations in blood glucose [17]. Many studies have explained the diabetogenic effect of SARS-CoV-2. It binds to ACE2 receptors located in many key metabolic organs which are involved in the glucose metabolism [8,9].

Multiple organs such as kidneys, heart, testis, lungs, pancreas, bladder, stomach, ileum, and liver express ACE2 receptors, which may explain the multiple organ failure seen in some COVID-19 patients. [10,11].

It has been hypothesized that the COVID-19 might affect pancreatic B-cells to produce insulin as well as the destruction of hepatocytes which causes insulin resistance. This leads to an acute hyperglycemic crisis that requires high-dose insulin to regulate, especially in patients with moderate or severe clinical presentation.

The use of corticosteroids to reduce inflammation in lung disease resulting with acute respiratory distress syndrome has long been known in clinical practice. In COVID-19 infection there is often excessive systemic inflammation and multi-organ dysfunction.

However, the efficacy of corticosteroids in virus-related diseases, is doubtful. An Expert Consensus on the Use of Corticosteroid in Patients with 2019-nCoV Pneumonia in China mentioned the dispute and controversy about corticosteroid usage for patients with COVID-19 and suggested that glucocorticoids should be administered with caution, especially in diabetic patients [12].

During the last two years many opposed results regarding corticosteroid-therapy in COVID-19 disease were published. The RECOVERY trial found that dexamethasone 6 mg once per day for 10 days reduced deaths by one-third in ventilated patients and by one-fifth in other patients, receiving oxygen therapy, although there was no benefit among patients who did not require respiratory support [3].

At the other hand, low-dose (30–80 mg/day), short-term (3–5 days) methylprednisolone is also a common treatment protocol, which was derived from the lesson of the severe acute respiratory syndrome (SARS) epidemic some years ago.

A study from Liu K et al, conducted in Hubei Province in China, showed that low-dose, short-term systemic corticosteroid therapy does not show significant benefits in outcome of pulmonary disease [13].

MetCOVID randomised controlled trial conducted in Brazil showed lower mortality in patients over 60 years of age with COVID-19 infection who were treated with short-term methylprednisolone. But the investigator group do not recommend use of steroids in less severe patients, or younger patients, suggesting that it can induce more harm than benefit [14].

In our study we observed the diabetic status in patients receiving corticosteroid therapy, according to the hospital protocol between December 2020 and May 2021.

Most of the patients were treated with pulse doses of methylprednisolone (61,6%), and 15,7% were treated with dexamethasone. We found significant difference in worsening of glycemic control in patients treated with methylprednisolone in comparison with patients treated with dexamethasone. Similar to the findings from the CORONA DO study our data show that COVID-19 patients with diabetes have a mortality rate which is twice that of non-diabetic patients [15].

Nevertheless, diabetes at admission couldn't be identified as an independent predictor of fatal outcome.

Significant mortality rate was found in those patients in whom worsening of glycoregulation was registered. According to data from our study worst clinical scenario is treatment with methylprednisolone in patient who starts showing deterioration of glycemic control.

While newly diagnosed diabetes in COVID-19 patients could be due to the stress response associated with severe illness or treatment with glucocorticoids, the diabetogenic effect of COVID -19 should also be considered. [5].

This is supported by reports showing exceptionally high insulin requirement in severely or critically ill COVID-19 patients with diabetes. In addition to impaired insulin secretion, COVID-19 patients also present with a high degree of insulin resistance, particularly those with severe illness [16].

Conclusion

Diabetes mellitus is a major comorbidity for COVID-19 infection, and one of the most common causes of poor prognosis in patients with pneumonia. Many therapies have been repurposed for the management of COVID-19.

According to the results of our study, we suggest that if corticosteroid therapy is necessary during treatment, it is safer to administer it with dexamethasone, especially in patients who have diabetes or are at risk to develop diabetes. As long as patients are treated with corticosteroids, care should be taken not to neglect its side effects.

Deterioration of glycoregulation and the need to replace oral antidiabetic therapy with insulin are common. It is also common for newly diagnosed diabetes to persist even after the patients have recovered from the COVID-19 disease.

References

1. Loganathan S , Kuppusamy M, Wankhar W et al. Angiotensin-converting enzyme 2 (ACE2): COVID 19 gate way to multiple organ failure syndromes, Respir Physiol Neurobiol. 2021 Jan;283: 103548.doi: 10.1016/j.resp.2020.103548. Epub 2020 Sep 18.
2. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev. 2016;3:CD010406. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26950335.
3. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. N Engl J Med. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.
4. Mareev VY, Orlova YA, Pavlikova EP et al; Steroid pulse -therapy in patients with coronavirus pneumonia (COVID-19), systemic inflammation and risk of venous thrombosis and thromboembolism (WAYFARER Study) Kardiologija 2020 Jul 7;60(6): 15-29. doi: 10.18087/cardio.2020.6.n1226.
5. Romanou V, Koukaki E, Chantziara V, et al; Dexamethasone in the Treatment of COVID 19: Primus Inter Pares? Journal of personalized medicine 2021 Jun 15;11(6):556. doi: 10.3390/jpm11060556.

6. World health organization;Clinical management of COVID-19: interim guidance, 27 May 2020
7. Zhao JP, Hu Y, Du RH, Chen ZS, Jin Y, Zhou M et al (2020) Expert consensus on the us of corticosteroid in patients with 2019-nCoV pneumonia. ZhonghuaJie He He Hu Xi ZaZhi 43: 183–184.
8. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP et al (2020) Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J 133:1025–1031
9. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; Metcovid): a randomized, double-blind, Phase IIb, placebo-controlled trial. Clin Infect Dis. 2021 May 4;72(9):e373-e381.
10. Saqib A, Solanki P, Carroll M, Gough A, Oguntolu V. Impact of COVID-19 on glycaemic control: a retrospective cohort study in a local district general hospital. Pract Diabetes. 2020;37(5):164–7.
11. Ceriello A. Hyperglycemia and COVID-19: What was known and what is really new? Diabetes Res Clin Pract [Internet]. 2020 Aug 25 [cited 2020 Sep 16]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7445137/.
12. Gembardt F, Sterner-Kock A, Imboden H, et al. Organ-specific distribution of ACE2 mRNA and correlating peptidase activity in rodents. Peptides. 2005;26(7):1270-1277. This article is protected by copyright. All rights reserved. 66. Riordan JF. Angiotensin-I-converting enzyme and its relatives. Genome Biology. 2003;4(8):225.
13. Riordan JF. Angiotensin-I-converting enzyme and its relatives. Genome Biology. 2003;4(8):225.
14. Sathish T, Tapp RJ, Cooper ME, Zimmet P. Potential metabolic and inflammatory pathways between COVID-19 and new-onset diabetes. Diabetes Metab. 2020.
15. Scheen A.J., Marre M., Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: findings from the CORONADO study and other recent reports. Diabetes Metab. 2020;46(4):265–271.
16. 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.
17. Nassar M, Daoud A, Nso N, et al. Diabetes Mellitus and COVID-19: Review Article [published online ahead of print, 2021 Sep 4*]*. Diabetes Metab Syndr. 2021;15 (6):102268. doi:10.1016/j.dsx.2021.102268.