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Moderately hyperglycemia as an independent prognostic factor for the worse outcome of COVID-19

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ABSTRACT

Background: Blood sugar (BS) has been proposed as a prognostic factor for COVID-19. In this historical cohort study we evaluated the association between admission time BS and COVID-19 outcome.
Methods: First, hospitalized COVID-19 patients were divided into three groups; Non-diabetic patients with BS < 140 mg/dl (N = 394), non-diabetic patients with BS ≥ 140 mg/dl (N = 113) and diabetic patients (N = 315). Mortality, ICU admission, and length of hospital stay were compared between groups and odds ratio was adjusted using logistic regression.
Results: After adjustment with pre-existing conditions and drugs, it was shown that non-diabetic patients with BS ≥ 140 mg/dl are at increased risk of mortality (aOR 1.89 (0.99–3.57)) and ICU admission (aOR 2.62 (1.49–4.59)) even more than diabetic patients (aOR 1.72 (1.07–2.78) for mortality and aOR 2.28 (1.47–3.54) for ICU admission.
Conclusions: Admission time hyperglycemia predicts worse outcome of COVID-19 and BS ≥ 140 mg/dl is associated with a markedly increase in ICU admission and mortality.

1. Introduction

Since the beginning of the COVID-19 pandemic, a growing concern raised surrounding the management of health care systems [1]. Shortage of facilities during surge of the pandemic necessitates patients screening to identify patients with severe disease. This contributes to cautiously allocate ventilators and other facilities according to priorities [2]. Prognostic factors are widely used for different diseases to predict the outcome of diseases and modulate it by early intervention [3]. Previous studies attempted to introduce several prognostic factors to identify COVID-19 patients, at high risk of severe outcome. Herein, it was observed that increased C-reactive protein (CRP), lactate dehydrogenase (LDH) and D-dimer and decreased platelet count and lymphocyte count are associated with poor outcome of COVID-19 [4]. Similarly, increased ferritin and prolactin prognosticate severe COVID-19 [5].

Diabetes is a risk factor for poor outcome of several diseases such as cardiovascular diseases, cancers and infectious diseases [6]. In addition, diabetes increases the risk of infectious diseases, particularly among older people [7]. There is a bidirectional relationship between hyperglycemia and infection. Hyperglycemia can weaken effective immune response to pathogens [8]. In exchange, extensive release of inflammatory cytokines and stress hormones during infection and other inflammatory diseases induces insulin resistance and hyperglycemia [9]. However, stress hyperglycemia has been proposed as an essential protective mechanism [9]. Better glycemic control decreases the risk of infection [7]. Diabetes and hyperglycemia are common findings among COVID-19 patients and they are associated with worse outcomes of COVID-19 [10]. In this historical cohort study, we compared COVID-19 outcomes between diabetic patients, non-diabetic patients with hyperglycemia and non-diabetic patients without hyperglycemia. Next, we assessed which range of admission time BS is associated with worst outcome of COVID-19. It is the first study that reports the most dangerous zone of admission time BS for COVID-19.

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2. Methods and materials

2.1. Study population and source of data

This retrospective study was performed in Baharloo Hospital, Tehran. Hospitalized COVID-19 patients, entered this historical cohort study. According to the type of study, which was a cross-sectional analysis, the sample size was not calculated for each group and all patients who had the desired parameters were included. These patients were admitted between March 25, 2020 and October 25, 2020. Patients' files were source of data for this study. All patients were hospitalized because of their severe signs and symptoms and a documented PCR or CT-scan, in favor of COVID-19. Patients with at least one of the following conditions were admitted; PaO_2/FiO_2 less than 300, more than 50% involvement of the lungs in the chest radiography (chest X-Ray or CT scan), clinical manifestations of dyspnea such as labored and shallow breathing and particularly tachypnea (more than 30 breathes per minute), inability to eat because of severe digestive symptoms and cardiovascular instability. Patients younger than 20 years of age were excluded from this study. A small group of patients received intravenous immunoglobulin (IVIG), remdesivir, interferon-β (INF-β), tocilizumab, hemoperfusion and extracorporeal membrane oxygenation (ECMO) during their hospitalization. These patients were excluded (N = 12). As blood sugar at the time of admission was part of groups' definition, patients without admission time blood sugar were excluded (N = 70), as well. Patients' informed consents were obtained before using their files as the source of data for this study. Ethical standards explained in the 2013 Declaration of Helsinki, were considered in the designation of this study. Additionally, the ethics committee of Tehran University of Medical Sciences (TUMS) completely evaluated the method of our study, approved it and granted the code, IR.TUMS.VCR.REC.1399.148.

3. Treatment protocol

Respiratory support and hydration were provided. Intubation was performed for patients without sufficient response to nasal O_2 or NIV (non-invasive ventilation). Symptomatic management was considered for fever, pain, vomiting and diarrhea. Use of anti-inflammatory and anti-viral drugs with significantly different distribution among groups, has been adjusted for assessment of odds ratio.

4. Groups of patients and outcomes

First of all, we divided patients into three groups, diabetic patients, non-diabetic patients with admission time BS < 140 mg/dl and non-diabetic patients with admission time BS ≥ 140 mg/dl [11,12]. Our definition for diabetes was based on patients' histories. Death, ICU admission, length of hospital stay were compared between groups as the outcomes of this study. In addition, crude odds ratio and adjusted odds ratio were assessed for these outcomes.

5. Data analysis

Quantitative traits are shown as mean (SD) and qualitative traits are presented as frequencies and percentages. Differences in means were evaluated by student's t-test. Differences in percentages were measured by chi-square test. Data were analyzed by Stata software version 14 and p value < 0.05 was considered significant. Logistic regression was used for adjustment of odds ratio. In order to recognize the confounders, we assessed the demographic features of each group such as age, sex and body mass index (BMI). Further, we compared their pre-existing conditions such as cardiovascular diseases (defined as ischemic heart diseases, congestive heart failure and valvular heart diseases), hypertension, diabetes, stroke, smoking, malignancy, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis, chronic kidney disease (CKD), systemic lupus erythematous, rheumatoid arthritis, dyslipidemia and thyroid diseases (hypo- and hyperthyroidism). Demographic features, comorbidities and drugs with significantly different distribution among groups, were used for adjustment of odds ratio.

6. Results

According to our inclusion criteria, 822 patients entered this study. Among them, 394 non-diabetic patients with admission time BS < 140 mg/dl entered group 1, 113 non-diabetic patients with admission BS ≥ 140 mg/dl entered group 2 and 315 patients with history of diabetes entered group 3. Their age was 57.52 ± 16.79 years and diabetic patients were significantly older. The average BMI of studied patients was 27.58 (± 5.70). Hypertension, cardiovascular diseases, dyslipidemia, CKD and use of corticosteroids and ACE inhibitors and ARBs had significantly different distribution among groups and were used for adjustment of odds ratio. All of these conditions were more common among diabetic patients but the conditions had similar prevalence in the other groups. However, respiratory disease showed non-significant difference among groups, but because of their impact on COVID-19

Table 1
Patients' co-existing conditions and types of medication used for them.

	All patients (n = 822)	Group 1 (N = 394)	Group 2 (N = 113)	Group 3 (n = 315)	P value
Age	57.52 ± 16.79	53.85 ± 17.73	53.67 ± 16.52	63.49 ± 13.72	< 0.0001
BMI	27.58 ± 5.70	27.35 ± 4.81	26.75 ± 3.78	28.08 ± 6.90	0.175
Male	461 (56.1)	227 (57.6)	69 (61.1)	165 (52.4)	0.195
Age > 60 years	369 (44.9)	142 (36)	38 (33.6)	189 (60)	< 0.0001
Hypertension	281 (34.2)	78 (19.8)	20 (17.7)	183 (58.1)	< 0.0001
Stroke	58 (7.1)	24 (6.1)	9 (8)	25 (7.9)	0.585
Current or former smoker (n = 609) Ψ	62 (7.5)	23 (5.8)	11 (9.7)	28 (8.9)	0.198
Dyslipidemia	51 (6.2)	15 (3.8)	1 (0.9)	35 (11.1)	< 0.0001
Cardiovascular diseases †	131 (15.9)	46 (11.7)	16 (14.2)	69 (21.9)	0.001
Thyroid diseases ‡	32 (3.9)	13 (3.3)	3 (2.7)	16 (5.1)	0.364
Respiratory diseases ¶	38 (4.6)	17 (4.3)	10 (8.8)	11 (3.5)	0.062
Rheumatologic diseases §	9 (1.1)	4 (1)	1 (0.9)	4 (1.3)	0.924
CKD	24 (2.9)	10 (2.5)	0	14 (4.4)	0.045
Bilastinum	357 (43.4)	182 (46.2)	41 (36.3)	134 (42.5)	0.159
Ribavirin	134 (16.3)	60 (15.2)	21 (18.6)	53 (16.8)	0.661
Corticosteroids	141 (17.2)	54 (13.7)	19 (16.8)	68 (21.6)	0.022
ACE inhibitors/ARB	90 (10.9)	25 (6.3)	10 (8.8)	55 (17.5)	< 0.0001
PPI	381 (46.4)	179 (45.4)	50 (44.2)	152 (48.3)	0.672

Footnote: Group 1: Non-diabetic patients with BS < 140 mg/dl. Group 2: Non-diabetic patients with BS ≥ 140 mg/dl. Group 3: Diabetic patients. Data are presented as number (percentage). Age and BMI are shown as mean (SD). † Cardiovascular diseases were defined as ischemic heart diseases, congestive heart disease, valvular heart diseases, stoke and peripheral vascular disease. ‡ Thyroid diseases were defined as hypothyroidism and hyperthyroidism. ¶ Respiratory diseases were considered as COPD, tuberculosis and asthma. § Rheumatologic diseases were defined as systemic lupus erythematous and rheumatoid arthritis. Ψ Smoking data were available for 609 patients. Angiotensin-converting enzyme (ACE), angiotensin receptor blocker (ARB), body mass index (BMI), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), proton pump inhibitor (PPI).

outcomes, they were used for adjustment of odds ratio (Table 1). Of all patients, 15.1% died after hospitalization and 19.8% were admitted to ICU. Mortality was significantly higher in group 3 than group 2. Group 1 had significantly lower mortality rate Fig. 1). ICU admission followed the same pattern. Diabetic patients had significantly longer length of hospital stay (Table 2).

According to crude odds ratio, diabetes was associated with increased mortality (95% CI, OR 2.19 (1.43–3.35), $p < 0.0001$), ICU admission (95% CI, OR 3.02 (2.04–4.48), $P < 0.0001$) and length of hospital stay (95% CI, OR 1.57 (1.15–2.16), $p = 0.005$). Further, non-diabetic patients with BS $\geq$ 140 mg/dl had increased risk of ICU admission (95% CI, OR 2.37 (1.39–4.03), $p = 0.001$) and partly mortality (95% CI, OR 1.74 (0.96–3.13), $p = 0.066$). After adjustment of odds ratio with age and sex, it was shown that non-diabetic patients with BS $\geq$ 140 mg/dl had worst outcomes, according to mortality (95% CI, aOR 1.92 (1.04–3.58), $p = 0.038$) and ICU admission (95% CI, aOR 2.57 (1.48–4.46), $p = 0.001$). Increased mortality (95% CI, aOR 1.62 (1.04–2.53), $p = 0.032$) and ICU admission (95% CI, aOR 2.45 (1.63–3.69), $p < 0.0001$) were also observed among diabetic patients but lower than group 2. However, even after adjustment of age and sex just diabetes was associated with increased length of hospital stay (95% CI, aOR 1.55 (1.11–2.15), $p = 0.009$). After multiple adjustment of odds ratio with age, sex, hypertension, cardiovascular, respiratory diseases, CKD, corticosteroids, ARBs and ACE inhibitors, it was shown that BS $\geq$ 140 mg/dl among non-diabetic patients considerably increased mortality (95% CI, aOR 1.89 (0.99–3.57), $p = 0.050$) and ICU admission (95% CI, aOR 2.62 (1.49–4.59), $p = 0.001$) but could not significantly affect length of hospital stay. Diabetes was associated with increased mortality (95% CI, aOR 1.72 (1.07–2.78), $P = 0.026$) and ICU admission (95% CI, aOR 2.28 (1.47–3.54), $p < 0.0001$) but its impact on mortality and ICU admission was lower than BS $\geq$ 140 among non-diabetic patients. In addition, after multiple adjustment, it was revealed that diabetes could not significantly increase length of hospital stay (Table 3).

7. Discussion

Since the outbreak of COVID-19 in Wuhan, China several prognostic factors have been proposed to predict the outcome of COVID-19 [5,13]. Diabetes is a prevalent comorbidity of COVID-19 and previous studies, consistent with this study, indicated that diabetes predicts poor outcome of COVID-19 [14,15]. Previously, it was uncovered that hyperglycemia and diabetes are independent predictors for death in severe acute respiratory syndrome (SARS) patients [16]. It was shown that higher level of admission time BS predicts poor outcome of COVID-19. Similarly, increase of BS after during hospital stay was associated with severe outcome of COVID-19 [17]. It was reported that hyperglycemia is

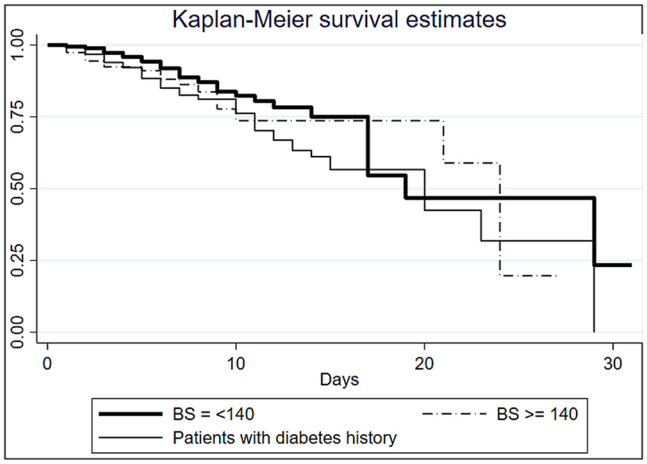

Fig. 1. Patients' survival after admission.

Table 2
Mortality, ICU admission, and length of in hospital stay among groups.

	All patients (N = 822)	Group 1 (N = 394)	Group 2 (N = 113)	Group 3 (N = 315)	P value
Death	124 (15.1)	41 (10.4)	19 (16.8)	64 (20.3)	0.001
ICU admission	163 (19.8)	46 (11.7)	27 (23.9)	90 (28.6)	< 0.0001
median length of hospital stay (days)	6 (5)	6 (5)	6 (5.5)	7 (5)	0.003

Footnote: Group 1: Non-diabetic patients with BS < 140 mg/dl. Group 2: Non-diabetic patients with BS $\geq$ 140 mg/dl. Group 3: Diabetic patients. Death and ICU admission are presented as number (percentage) and median length of stay is presented as median (interquartile range).

associated with worse outcome of COVID-19, compared with diabetes. Further, it was reported that hyperglycemia prolongs length of hospital stay and markedly increases mortality [18]. Wang et al. reported that fasting blood sugar (FBS) $\geq$ 7 mmol (126 mg/dl) at admission predicts lower survival of patients [19]. Li et al. found that newly diagnosed diabetes is associated with the worst outcomes followed by known diabetes and hyperglycemia, respectively [20].

Severe acute respiratory coronavirus 2 (SARS-CoV-2) stimulates immune system and promotes the release of numerous pro-inflammatory cytokines [21]. The pro-inflammatory metabolic state can induce severe insulin resistance which results in hyperglycemia [22]. Previous studies uncovered the molecular mechanisms which mediates insulin resistance in hepatocytes during cytokine storm [23]. Moreover, chronic inflammation has been implicated in insulin resistance [24]. Hyperglycemia is associated with higher concentrations of interleukin 6 (IL6) and D-dimer in patients with COVID-19 [25,26]. This can show that hyperglycemia is a sign of underlying cytokine storm which is associated with poor prognosis of COVID-19. Hyperglycemia and diabetes increase urinary excretion of ACE2 [27]. Likewise, ACE2 expression increases in animal model of diabetes [28,29]. SARS-CoV-2 uses ACE2 for its entry into the host cells and upregulation of ACE2 can lead to higher viral load [30,31]. Further, ACE2 is vigorously expressed in the pancreas and SARS-CoV-2 can invade pancreatic islets [32]. This may result in insufficient insulin secretion and hyperglycemia.

In our study, non-diabetic patients with BS $\geq$ 140 mg/dl had the worst outcomes regarding mortality and ICU admission. Likewise, diabetes was associated with worse outcomes and increase in mortality and ICU admission. Moreover, it was shown that BS $\geq$ 140 mg/dl independently was associated with increase in mortality and ICU admission, regardless of the presence or absence of diabetes. However, parts of our results were not statistically significant because of inadequate power of this study.

8. Conclusion

Taken together, this study indicated that admission time BS $\geq$ 140 mg/dl predicts higher mortality and ICU admission among hospitalized COVID-19 patients. Moreover, mortality and ICU admission were more common among non-diabetic patients with admission time BS $\geq$ 140 mg/dl, even more than diabetic patients.

Limitations

Our investigation is a cross-sectional study and encountered several hurdles such as low sample size, lack of general medication detail of patients, lack of patient BMI information, and we relied on the histories of patients for parts of the data.

Table 3
Odds ratio for outcomes of COVID-19 among three groups of patients.

Outcome: Death						
	Model 1 odds ratio	P-value	Model 2 odds ratio	P-value	Model 3 odds ratio	P-value
Group 1	1		1		1	
Group 2	1.74 (0.96–3.13)	0.066	1.92 (1.04–3.58)	0.038	1.89 (0.99–3.57)	0.050
Group 3	2.19 (1.43–3.35)	< 0.0001	1.62 (1.04–2.53)	0.032	1.72 (1.07–2.78)	0.026
Outcome: ICU Admission						
Group 1	1		1		1	
Group 2	2.37 (1.39–4.03)	0.001	2.57 (1.48–4.46)	0.001	2.62 (1.49–4.59)	0.001
Group 3	3.02 (2.04–4.48)	< 0.0001	2.45 (1.63–3.69)	< 0.0001	2.28 (1.47–3.54)	< 0.0001
Outcome: Increased length of hospital stay (more than median)						
Group 1	1		1		1	
Group 2	1.21 (0.78–1.88)	0.375	1.21 (0.78–1.88)	0.412	1.19 (0.77–1.86)	0.442
Group 3	1.57 (1.15–2.16)	0.005	1.55 (1.11–2.15)	0.009	1.30 (0.91–1.85)	0.140

Model 1: Without adjustment; Model 2: Adjustment of odds ratio with age and sex; model 3: Multiple adjustment of odds ratio with age, sex, hypertension, cardiovascular diseases, respiratory diseases, CKD, corticosteroids, ARB and ACE inhibitors). For all outcomes, 95% confidence of interval (CI) was considered for assessment of odds ratio.
Group 1: Non-diabetic patients with BS < 140 mg/dl (N = 394). Group 2: Non-diabetic patients with BS ≥ 140 mg/dl (N = 113). Group 3: Diabetic patients (N = 315).
ACE (angiotensin-converting enzyme), ARB (angiotensin receptor blocker), CKD (chronic kidney diseases).

Ethical approval

This study was conducted in accordance with the 2013 version of the Declaration of Helsinki and was approved by the ethics committee of Tehran University of Medical Sciences (TUMS). The ethics committee of Tehran University of Medical Sciences (TUMS) measured the method of this study and approved it, IR.TUMS.VCR.REC.1399.148.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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References

[1] J.G. Adams, R.M. Walls, Supporting the health care workforce during the COVID-19 global epidemic, JAMA 323 (15) (2020) 1439–1440.
[2] G. Grasselli, A. Pesenti, M. Cecconi, Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response, JAMA 323 (16) (2020) 1545–1546.
[3] R.D. Riley, et al., Prognosis research strategy (PROGRESS) 2: prognostic factor research, PLOS Med. 10 (2) (2013), e1001380.
[4] X. Zhao, et al., Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis, MedRxiv (2020).
[5] I. Huang, et al., C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis, Ther. Adv. Respir. Dis. 14 (2020), 1753466620937175.
[6] F. Bragg, et al., Association between diabetes and cause-specific mortality in rural and urban areas of China, JAMA 317 (3) (2017) 280–289.
[7] J. Pearson-Stuttard, et al., Diabetes and infection: assessing the association with glycaemic control in population-based studies, Lancet Diabetes Endocrinol. 4 (2) (2016) 148–158.
[8] N. Jafar, H. Edriss, K. Nugent, The effect of short-term hyperglycemia on the innate immune system, Am. J. Med. Sci. 351 (2) (2016) 201–211.
[9] P.E. Marik, R. Bellomo, Stress hyperglycemia: an essential survival response!, Crit. Care 17 (2) (2013) 305.
[10] E. Selvin, S.P. Juraschek, Diabetes epidemiology in the COVID-19 pandemic, Diabetes Care 43 (8) (2020) 1690–1694.
[11] A.R. Saand, et al., Does inpatient hyperglycemia predict a worse outcome in COVID-19 intensive care unit patients? J. Diabetes 13 (3) (2021) 253–260.
[12] H. Permana, et al., The association of admission random blood glucose concentration and body-mass index with mortality in COVID-19 patients, Eur. Rev. Med. Pharmacol. Sci. 25 (22) (2021) 7144–7150.
[13] Y. Liu, et al., Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19, J. Infect. (2020).
[14] M. Apicella, et al., COVID-19 in people with diabetes: understanding the reasons for worse outcomes, Lancet Diabetes Endocrinol. (2020).
[15] J. Seiglie, et al., Diabetes as a risk factor for poor early outcomes in patients hospitalized with COVID-19, Diabetes Care 43 (12) (2020) 2938–2944.
[16] J.K. Yang, et al., Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS, Diabet. Med. 23 (6) (2006) 623–628.
[17] C. Sardu, et al., Hyperglycaemia on admission to hospital and COVID-19, Diabetologia 63 (11) (2020) 2486–2487.
[18] B. Bode, et al., Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States, J. Diabetes Sci. Technol. (2020), 1932296820924469.
[19] S. Wang, et al., Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study, Diabetologia 63 (10) (2020) 2102–2111.
[20] H. Li, et al., Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19, Diabetes, Obes. Metab. (2020).
[21] N. Vaninov, In the eye of the COVID-19 cytokine storm, Nat. Rev. Immunol. 20 (5) (2020) (277-277).
[22] R. Gianchandani, et al., Managing hyperglycemia in the COVID-19 inflammatory storm, Diabetes 69 (10) (2020) 2048–2053.
[23] P.J. Klover, et al., Chronic exposure to interleukin-6 causes hepatic insulin resistance in mice, Diabetes 52 (11) (2003) 2784–2789.
[24] H. Yang, et al., Obesity increases the production of proinflammatory mediators from adipose tissue T cells and compromises TCR repertoire diversity: implications for systemic inflammation and insulin resistance, J. Immunol. 185 (3) (2010) 1836–1845.
[25] C. Sardu, et al., Outcomes in patients with hyperglycemia affected by Covid-19: can we do more on glycemic control? Diabetes Care (2020).
[26] A. Coppelli, et al., Hyperglycemia at hospital admission is associated with severity of the prognosis in patients hospitalized for COVID-19: the Pisa COVID-19 Study, Diabetes Care 43 (10) (2020) 2345–2348.
[27] D.Z.I. Cherney, et al., Urinary ACE2 in healthy adults and patients with uncomplicated type 1 diabetes, Can. J. Physiol. Pharmacol. 92 (8) (2014) 703–706.
[28] H. Roca-Ho, et al., Characterization of ACE and ACE2 expression within different organs of the NOD mouse, Int. J. Mol. Sci. 18 (3) (2017) 563.
[29] J. Wysocki, M. Ye, M.J. Soler, S.B. Gurley, H.D. Xiao, K.E. Bernstein, T.M. Coffman, S. Chen, D. Batlle, ACE and ACE2 activity in diabetic mice, Diabetes 55 (2006) 2132–2139.
[30] A. Ali, R. Vijayan, Dynamics of the ACE2–SARS-CoV-2/SARS-CoV spike protein interface reveal unique mechanisms, Sci. Rep. 10 (1) (2020) 1–12.
[31] Q. Wang, et al., Structural and functional basis of SARS-CoV-2 entry by using human ACE2, Cell (2020).
[32] F. Liu, et al., ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection, Clin. Gastroenterol. Hepatol. (2020).