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The patient-centered diabetes management during the COVID-19 pandemic

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Abstract: Since December 2019, in the fight against the coronavirus disease 2019 (COVID-19) pandemic, we observed that glycemic control in people with diabetes is easily affected by lifestyle changes. To maintain a good health condition, a patient-centered approach with mental support and close monitoring is required. For these, telemedicine and online continuous glucose monitoring (CGM), are effective systems. Therefore, based on our experience during the two-year period, we reviewed the literature for appropriate actions required for the management of diabetes to prevent COVID-19 infection and avoid unfavorable outcomes in COVID-19 cases. Once infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there is a high risk of a poor prognosis in patients with diabetes. Glucocorticoid therapy in severe COVID-19 cases leads to further hyperglycemia. Since good glycemic control has been shown to improve outcomes, strict glycemic control using CGM is recommended. Using CGM data, insulin can be adequately titrated without causing hypoglycemia, and remote data monitoring can reduce the risk of infection for health care professionals, by reducing the frequency of patient contact. Among patients with COVID-19, some are found to have newly-diagnosed diabetes at admission. Those newly diagnosed patients present with a higher risk of poor prognosis compared to those with pre-existing diabetes. Therefore, glycemic status should be evaluated in all patients with COVID-19 admitted to hospitals.

Keywords: glycemic control, lifestyle change, prognosis, insulin, continuous glucose monitoring (CGM)

Introduction

During the COVID-19 pandemic, the management of diabetes has become a challenging task in some patients partly due to lifestyle changes imposed by the pandemic. Studies have shown that patients with diabetes in general present with excess mortality due to infectious diseases and their complications (*1*). In patients with COVID-19 and diabetes, if their glycemic control is worsened, they may have a poor prognosis and high mortality. Based on the reports thus far, diabetes does not appear to increase the risk of contracting SARS-CoV; however, when infected, the risk of hospitalization, intensive care unit (ICU) admission, and mortality increase (*2,3*). When patients with diabetes are managed with good glycemic control for a long period, the risk of developing severe COVID-19 is reduced (*4*).

In this review, based on our experience of the last two years and literature search, we describe the management of diabetes, to prevent COVID-19 infection and avoid unfavorable outcomes in COVID-19 cases.

Diabetes management taking into consideration the lifestyle changes during the COVID-19 pandemic

Since the onset of COVID-19 in 2019, the pandemic has caused changes in lifestyle, with people experiencing lockdown and teleworking. Changes in behavioral patterns had a significant impact on the self-management of diabetes. Due to lifestyle restrictions, body weight gain, reduced physical activity, and changes in eating habits affected glycemic control (*5-9*). Table 1 summarizes the results of past studies conducted to monitor changes in hemoglobin A1c (HbA1c) and body weight before and during the COVID-19 pandemic.

The effects of lifestyle changes on glycemic control during the COVID-19 pandemic in patients with diabetes (n = 321) were studied at our institution (*5*). The overall HbA1c levels showed no significant difference before and during the COVID-19 pandemic. However, although the number was small, there were patients with extreme deterioration in HbA1c level (median [interquartile range]; 0.1 [-0.30, 0.37]) who required adjustment and intensification of their diabetes management. Remote working was associated with an increase in HbA1c levels, accompanied by reduced physical activity and exercise. Notably, people living with companion animals such as dogs, who had unchanged regular walking habits, maintained their glycemic control.

Table 1. Effect of lifestyle changes before and during the COVID-19 pandemic

			Before COVID-19 pandemic		During COVID-19 pandemic	
Terakawa A, *et al*., J Diabetes Investig. 2022 (*5*)			Mean	SD	Mean	SD
n = 321	HbA1c (%)		7.13	0.98	7.18	0.98
	BW (kg)		69.2	14.9	68.9	14.9
	BMI (kg/m^2)		25.6	4.5	25.4	4.5
			Before declaration of state of emergency		After declaration of state of emergency	
Tanaka N, *et al*., J Diabetes Investig. 2021 (*6*)			Median	IQR	Median	IQR
n = 463	HbA1c (%)		7.5	1.3	7.3	1.3
	BW (kg)		68.7	18.9	68.5	18.4
			Before lockdown		During lockdown	
Ruissen MM, *et al*., BMJ Open Diabetes Res Care. 2021 (*8*)			Mean	SD	Mean	SD
n = 435[#]	HbA1c (%)		7.68	1.2	7.52	1.1
			Pre-lockdown		Post-lockdown	
Sanker P, *et al*., Diabetes Metab Syndr. 2020 (*10*)			Mean	SD	Mean	SD
n = 110	HbA1c (%)		8.2	1.3	8.12	1.6
	BW (kg)		71.5	14.8	71.8	13.6
			Pre-lockdown		Post-lockdown	
Khare J, *et al*., Prim Care Diabetes. 2021 (*9*)			Mean	Range	Mean	Range
n = 307	HbA1c (%)	M	7.85	6.1-13.0	8.37[*]	6.0-15.0
		F	8.03	6.3-15.0	8.52[*]	6.6-15.0
	BW (kg)	M	76.8	55-108	77.5	55-106
		F	68.9	54-110	70.1	57-111

BMI, body mass index; BW, body weight; COVID-19, coronavirus diseases 2019; IQR, interquartile range; SD, standard deviation; M, male; F, female. [#]Analysis was conducted in patients with type 1 diabetes. [*]$p < 0.05$.

In another study on Japanese patients with diabetes (*n* = 463), glycemic control was compared before and after the state of emergency declared by the Japanese government in the Spring of 2020 (*6*). Similar to the previous study, there were no changes in the median HbA1c level; however, the study showed that body weight gain was associated with HbA1c increase. In younger adults (< 65 years), changes in eating habits increased body weight and aggravated HbA1c levels. In older adults (≥ 65 years), reduced daily activity was associated with decreased body weight indicating loss of muscle mass.

In a study conducted in the Netherlands (*n* = 435), lockdown measures during the COVID-19 pandemic resulted in body weight gain, reduced exercise, and increased stress and anxiety in patients with diabetes (*8*). Despite these changes, no deterioration in overall glycemic control was observed. The study emphasized that increased stress is associated with difficulty in glycemic control. In another study conducted in South India on patients with type 2 diabetes (*n* = 110), the lockdown did not cause changes in glycemic control and body weight; however, increased psychosocial stress was observed, especially in women and older adults (*10*).

Psychological well-being in people with diabetes has been increasingly recognized as an important factor in maintaining better glycemic control (*11,12*). Psychological stress can simultaneously be a risk factor for the onset of metabolic disorder and a prognostic factor in diabetes. Although there are recommendations for the management of diabetes during the COVID-19 pandemic in terms of glycemic control targets and maintaining healthy lifestyles (*13,14*), they are not focused on psychological issues. The healthcare professionals need to design an approach to reduce psychosocial stress during pandemics, as well as manage diabetic conditions.

In the previous studies, there were no prominent changes in glycemic control during the COVID-19 pandemic; however, other reports have shown an increase in HbA1c levels (*9,15*). The setting of each study, including the duration of lockdown, medical conditions during the pandemic, and ethnicity, need to be considered when comparing theses contrasting

Table 2. Glycemic control and clinical outcomes in patient with COVID-19 and diabetes

Zhu L, *et al*., Cell Metab, 2020 (*20*)	Well controlled (*n* = 282) BG 70-180 mg/dL	Poorly controlled (*n* = 528) BG >180 mg/dL[1)]	*p* value
BG (IQR) (mg/dL)	115 (94-135)	196 (137-257)	< 0.001
In-hospital management			
Systemic corticosteroids, *n* (%)	57 (20.2%)	184 (34.9%)	< 0.001
Invasive ventilation, *n* (%)	0 (0.0%)	22 (4.2 %)	0.001
Well controlled *vs.* Poorly controlled	HR (95% CI)[2)]		
All-cause mortality	0.13 (0.04, 0.44)		< 0.001

Bode B, *et al*., J Diabetes Sci Technol, 2020 (*22*)	Diabetes and/or uncontrolled hyperglycemia[3)] (*n* = 184)	No diabetes and/or uncontrolled hyperglycemia (*n* = 386)	*p* value
Mean HbA1c (%)	8.5 ± 2.3	5.9 ± 0.51	< 0.001
Mean glucose (mg/dL)	178 ± 72.9	110.9 ± 22.6	< 0.001
Died in hospital	53 (28.8%)	24 (6.2%)	< 0.001
	Diabetes by HbA1c criteria (*n* = 88)	Uncontrolled hyperglycemia[3)] by BG (*n* = 96)	
Mean HbA1c (%)	9.1 ± 2.3	5.9 ± 0.4	< 0.001
Mean glucose (mg/dL)	177.8 ± 64.5	178.5 ± 78.9	0.704
Died in hospital	13 (14.8%)	40 (41.7%)	< 0.001

[1)]2 hr postprandial BG. [2)]Adjusted variables included age, gender, severity of COVID-19 and comorbidities. [3)]Uncontrolled hyperglycemia, defined as two or more BG measurements > 180 mg/dL in a 24-hour period with an HbA1c < 6.5% or no HbA1c available. BG, blood glucose; IQR, interquartile range; CI, confidence interval; HR, hazard ratio.

results. One study showed that the duration of lockdown was directly proportional to the worsening of glycemic control and diabetes-related complications (*15*). Healthcare professionals should be aware of certain high-risk cases, particularly patients with diabetes who require close monitoring, due to lifestyle changes that resulted in body weight increase, reduced exercise, and psychological stress, to prevent aggravation of the glycemic states. Telemedicine is a good strategy for maintaining communication with patients, for close follow-up, especially during stay-at-home periods. Recently, blood glucose monitoring (BGM) and continuous glucose monitoring (CGM) data can be stored on the web-based server, enabling remote monitoring of glycemic control. We need a patient-centered approach by a multidisciplinary medical team using these remote monitoring systems whenever necessary, to maintain healthy lifestyle practices and mental health under the restrictions of the COVID-19 pandemic.

Diabetes management under COVID-19 infection

As reported, there is a higher proportion of patients with diabetes among severe and ICU-admitted cases of COVID-19 than in mild cases (*16-18*). The cause of the poor prognosis can be multifactorial. In addition to hyperglycemia, older age, obesity, hypertension, cardiovascular disease, renal dysfunction, and pro-inflammatory and pro-coagulative states are considered to contribute to increased mortality and morbidity due to COVID-19 (*19*). In patients with diabetes comorbidity, any of these factors should be considered to reduce the risk of COVID-19.

Hyperglycemia is one of the main causes of poor prognosis and high mortality rate due to COVID-19 (*20-22*). Although diabetes is a risk factor, a recent study showed that when hyperglycemia is well-controlled, the risk for worse outcome can be reduced (Table 2) (*20*). A retrospective study conducted in China showed that the mortality rate was significantly lower in patients with well-controlled blood glucose levels (within 70-180 mg/dL) than in those with poorly-controlled blood glucose levels during hospitalization, (adjusted hazard ratio [HR] 0.14). This result suggests that even under diabetic conditions, well-controlled blood glucose levels may improve outcomes in patients with COVID-19.

Another retrospective study conducted in the U.S. showed that in-hospital mortality was significantly higher in people with diabetes and/or with uncontrolled hyperglycemia than in people without diabetes (Table 2) (*22*). Uncontrolled hyperglycemia is defined as two or more blood glucose measurements above 180 mg/dL in a 24-hour period, with a HbA1c less than 6.5%. In a subset analysis, patients with uncontrolled hyperglycemia had a particularly high mortality rate. This raises the important question of whether acute hyperglycemia can be a risk factor for poor outcomes in patients with COVID-19. The data show that better glycemic management will improve the outcome; therefore, close monitoring of blood glucose levels is essential in all patients with

COVID-19, regardless of their diabetes status.

These results provide us with important insights that must not be overlooked. In the COVID-19 ward, provision of care is challenging, with limited numbers of carers and protective equipment. Contact carers and healthcare professionals with patients need to be minimized. Under these constrained conditions, patients with no history of diabetes may not have their glucose levels frequently monitored. In the treatment of COVID-19, glucocorticoids are used in severe cases, which frequently causes acute hyperglycemia even in non-diabetic subjects. The results of previous studies strongly suggest that good glycemic control, below 180 mg/dL whenever possible, should be aimed to attain a better outcome in all patients.

In order to achieve this goal, CGM is an effective tool. Recent CGM can be remotely monitored, and frequent visits to patients and frequent point-of-care glucose testing can be safely minimized (*23*). In our institution, intermittently scanned CGM (isCGM) is used for severe COVID-19 patients with diabetes who require methylprednisolone therapy. The insulin dose was titrated as appropriate, without causing hypoglycemia, and better glycemic control was achieved (unpublished data). The daily glucose trend was remotely monitored by health care professionals, enabling a reduced frequency of patient contact. However, the use of the CGM system in COVID-19 wards is still limited to certain institutions and has not yet become widespread. Thus, there is an urgent need to develop a system in which any institution can easily introduce the CGM system to patients under this COVID-19 pandemic.

New-onset diabetes in COVID-19 patients

During the COVID-19 pandemic, a large number of COVID-19 patients developed diabetic ketoacidosis (DKA), ketosis, or hyperglycemic hyperosmolar syndrome (HHS). Data shows that DKA and combined DKA/HHS in patients with COVID-19 present with poor prognosis and high mortality rate (*24*). These metabolic disturbances may be caused by severe insulin resistance under viral infection combined with decreased insulin secretion due to b-cell dysfunction. Many reports have suggested a link between COVID-19 and diabetes (*13,25,26*).

The potential mechanism of metabolic disturbances in COVID-19 have been postulated. The major pathogenic mechanisms are systemic inflammation and immunological dysregulation induced by SARS-CoV-2 infection, which induces acute respiratory distress syndrome (ARDS), insulin resistance, hyperglycemia, vascular endothelial damage, thromboembolism, cardiovascular events, and disseminated intravascular coagulopathy (DIC) (*25*). In regard to metabolic disorder, renin-angiotensin system (RAS) is considered to play an important role in pancreatic b-cell dysfunction (*27*). In the diabetic state, the RAS is activated in the pancreas, and angiotensin II (AngII), downstream of the RAS, is strongly associated with islet dysfunction in experimental models. Angiotensin-converting enzyme 2 (ACE2) promotes the degradation of AngII into angiotensin (1-7) [Ang(1-7)] (*8,9*), and Ang(1-7) acts through the G protein-coupled receptor Mas and opposes many of the actions of AngII (*28,29*). The ACE2/Ang(1-7)/Mas axis serves as a protective and negative regulator of RAS (*30*). In COVID-19, ACE2 functions as an entry receptor for SARS-CoV-2 (*31*), and the infection breaks down the function of the ACE2/Ang(1-7)/Mas axis as a negative regulator of the RAS. However, whether this causes direct impact on pancreatic islets is still not clear and evidence is scant (*32,33*). There are discussions that this may not be the central pathogenic feature of COVID-19, and further study is awaited.

The direct effect of SARS-CoV-2 on b-cell function not only causes the deterioration of metabolic control in people with diabetes, but it is also speculated to lead to the development of new-onset diabetes (*19*). In a survey conducted at our institution, among the 62 patients with COVID-19 and diabetes, 19 (30.6 %) were newly-diagnosed at admission (*34*). It must be noted that in these patients with newly-diagnosed diabetes, plasma blood glucose levels were significantly higher three days after admission, and the severity of COVID-19 was significantly higher than that in patients with pre-existing diabetes. In another study of 102 patients with COVID-19 and diabetes, 21 (20.6%) were newly diagnosed with diabetes on admission (*35*). In a meta-analysis of eight studies, more than 3700 patients with COVID-19 and diabetes were included, and 14.4% were newly-diagnosed diabetes cases (*36*). In both studies, patients with newly diagnosed diabetes had higher blood glucose levels. These results strongly suggests that patients with COVID-19 need to be monitored for the presence of hyperglycemia and diabetes at admission, and newly diagnosed diabetes should be managed closely to prevent hyperglycemia and resultant worse outcomes.

Conclusion

We emphasize that patients with diabetes are vulnerable to lifestyle changes, which were observed during the current COVID-19 pandemic. A patient-centered approach is essential. Mental support, telemedicine, and the use of CGM to remotely monitor glycemic changes can be an effective tool to maintain healthy life styles and better glycemic control. Although diabetes is a risk factor for poor prognosis in patients with COVID-19, good glycemic management will lead to better outcomes. In the COVID-19 ward, CGM system is an effective and safe measure to maintain a balance between close glucose monitoring and adequate patient contact frequencies. Lastly, we must be aware that COVID-19 can deteriorate the metabolic system, and some cases

of newly-diagnosed diabetes occur in patients with COVID-19. Blood glucose levels should be examined and the state of diabetes should be carefully evaluated in all patients with COVID-19 at admission, so that treatment for hyperglycemia can be started without unnecessary delay.

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References

1. Zoppini G, Fedeli U, Schievano E, Dauriz M, Targher G, Bonora E, Corti MC. Mortality from infectious diseases in diabetes. Nutr Metab Cardiovasc Dis. 2018; 28:444-450.
2. CDC COVID-19 Response Team, Chow N, Fleming-Dutra K, Gierke R, Hall A, Hughes M, Pilishvili T, Ritchey M, Roguski K, Skoff T, Ussery E. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 - United States, February 12-March 28, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69:382-386.
3. Fadini GP, Morieri ML, Longato E, Avogaro DA. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest. 2020; 43:867-869.
4. Wang B, Glicksberg BS, Nadkarni GN, Vashishth D. Evaluation and management of COVID-19-related severity in people with type 2 diabetes. BMJ Open Diabetes Res Care. 2021; 9:e002299.
5. Terakawa A, Bouchi R, Kodani N, Hisatake T, Sugiyama T, Matsumoto M, Ihana-Sugiyama N, Ohsugi M, Ueki K, Kajio H. Living and working environments are important determinants of glycemic control in patients with diabetes during the COVID-19 pandemic: a retrospective observational study. J Diabetes Investig. 2022; 13:1094-1104.
6. Tanaka N, Hamamoto Y, Kurotobi Y, Yamasaki Y, Nakatani S, Matsubara M, Haraguchi T, Yamaguchi Y, Izumi K, Fujita Y, Kuwata H, Hyo T, Yamada Y, Kurose T, Seino Y. Lifestyle changes as a result of COVID-19 containment measures: Bodyweight and glycemic control in patients with diabetes in the Japanese declaration of a state of emergency. J Diabetes Investig. 2021; 12:1718-1722.
7. Ruiz-Roso MB, Knott-Torcal C, Matilla-Escalante DC, Garcimartín A, Sampedro-Nuñez MA, Dávalos A, Marazuela M. COVID-19 lockdown and changes of the dietary pattern and physical activity habits in a cohort of patients with type 2 diabetes mellitus. Nutrients. 2020; 12:2327.
8. Ruissen MM, Regeer H, Landstra CP, Schroijen M, Jazet I, Nijhoff MF, Pijl H, Ballieux BEPB, Dekkers O, Huisman SD, de Koning EJP. Increased stress, weight gain and less exercise in relation to glycemic control in people with type 1 and type 2 diabetes during the COVID-19 pandemic. BMJ Open Diabetes Res Care. 2021; 9:e002035.
9. Khare J, Jindal S. Observational study on effect of lock down due to COVID 19 on HBA1c levels in patients with diabetes: Experience from Central India. Prim Care Diabetes. 2021. S1751-9918(20)30362-4.
10. Sankar P, Ahmed WN, Mariam Koshy V, Jacob R, Sasidharan S. Effects of COVID-19 lockdown on type 2 diabetes, lifestyle and psychosocial health: A hospital-based cross-sectional survey from South India. Diabetes Metab Syndr. 2020; 14:1815-1819.
11. American Diabetes Association Professional Practice Committee; Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, Green J, Huang E, Isaacs D, Kahan S, Leon J. 5. Facilitating behavior change and well-being to improve health outcomes: standards of medical care in diabetes-2022. Diabetes Care. 2022; 45:S60-S82.
12. Hackett RA, Steptoe A. Type 2 diabetes mellitus and psychological stress - a modifiable risk factor. Nat Rev Endocrinol. 2017; 13:547-560.
13. Bornstein SR, Rubino F, Khunti K, *et al*. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020; 8:546-550.
14. Papadokostaki E, Tentolouris N, Liberopoulos E. COVID-19 and diabetes: What does the clinician need to know? Prim Care Diabetes. 2020; 14:558-563.
15. Ghosal S, Sinha B, Majumder M, Misra A. Estimation of effects of nationwide lockdown for containing coronavirus infection on worsening of glycosylated haemoglobin and increase in diabetes-related complications: A simulation model using multivariate regression analysis. Diabetes Metab Syndr. 2020; 14:319-323.
16. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; 75:1730-1741.
17. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020; 323:1061-1069.
18. Deng SQ, Peng HJ. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China. J Clin Med. 2020; 9:575.
19. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. 2020; 8:782-792.
20. Zhu L, She ZG, Cheng X, *et al*. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020; 31:1068-1077.
21. Li X, Xu S, Yu M, *et al*. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020; 146:110-118.
22. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, Klonoff DC. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol. 2020; 14:813-821.
23. Agarwal S, Mathew J, Davis GM, Shephardson A, Levine A, Louard R, Urrutia A, Perez-Guzman C, Umpierrez GE, Peng L, Pasquel FJ. Continuous glucose monitoring in the intensive care unit during the COVID-19 pandemic. Diabetes Care. 2021; 44:847-849.
24. Pal R, Banerjee M, Yadav U, Bhattacharjee S. Clinical profile and outcomes in COVID-19 patients with diabetic ketoacidosis: A systematic review of literature. Diabetes Metab Syndr. 2020; 14:1563-1569.
25. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and

diabetes mellitus: From pathophysiology to clinical management. Nat Rev Endocrinol. 2021; 17:11-30.
26. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract. 2020; 162:108142.
27. Tikellis C, Wookey PJ, Candido R, Andrikopoulos S, Thomas MC, Cooper ME. Improved islet morphology after blockade of the renin- angiotensin system in the ZDF rat. Diabetes. 2004; 53:989-997.
28. Danilczyk U, Penninger JM. Angiotensin-converting enzyme II in the heart and the kidney. Circ Res. 2006; 98:463-471.
29. Benter IF, Yousif MH, Cojocel C, Al-Maghrebi M, Diz DI. Angiotensin-(1-7) prevents diabetes-induced cardiovascular dysfunction. Am J Physiol Heart Circ Physiol. 2007; 292:H666-H672.
30. Lu CL, Wang Y, Yuan L, Li Y, Li XY. The angiotensin-converting enzyme 2/angiotensin (1-7)/Mas axis protects the function of pancreatic β cells by improving the function of islet microvascular endothelial cells. Int J Mol Med. 2014; 34:1293-1300.
31. Scialo F, Daniele A, Amato F, Pastore L, Matera MG, Cazzola M, Castaldo G, Bianco A. ACE2: The major cell entry receptor for SARS-CoV-2. Lung. 2020; 198:867-877.
32. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010; 47:193-199.
33. Kusmartseva I, Wu W, Syed F, *et al.* Expression of SARS-CoV-2 entry factors in the pancreas of normal organ donors and individuals with COVID-19. Cell Metab. 2020; 32:1041-1051.e6.
34. Uchihara M, Bouchi R, Kodani N, *et al.* Impact of newly diagnosed diabetes on COVID-19 severity and hyperglycemia. J Diabetes Investig. 2022. doi: 10.1111/jdi.13754.
35. Sathish T, Chandrika Anton M. Newly diagnosed diabetes in patients with mild to moderate COVID-19. Diabetes Metab Syndr. 2021; 15:569-571.
36. Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: A systematic review and meta-analysis. Diabetes Obes Metab. 2021; 23:870-874.

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