BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X.

Online ISSN 2357-0016

Correlation of COVID-19 and Development of New Onset Diabetes Mellitus and its Possible Pathogenesis

Medhat A. Khalil, Nabil khattab, Ali E. Ali, Ahmed M. Mostafa, Mohamed A. Mohamed

Internal Medicine Department, Faculty of Medicine Benha University, Egypt.

Corresponding to:
Dr. Ahmed M. Mostafa.
Internal Medicine Department, Faculty of Medicine Benha University, Egypt.
Email: drahmedaly6@gmail.com

Received:
Accepted:

Abstract:

Background: The severe acute respiratory syndrome-coronavirus (SARS-CoV)-2 was the cause of the pandemic known as coronavirus disease-19 (COVID-19). One of the main metabolic diseases that contribute to death and morbidity worldwide is diabetes. This study aims to evaluate the likelihood of developing new-onset diabetes mellitus in COVID-19-infected patients and its possible pathogenesis. **Patients and Methods:** This cross-sectional study was conducted at Ashmoun Fever Hospital and Menouf Fever Hospital on 100 patients with confirmed COVID-19 admitted and managed in an inpatient ward and isolated ICU department for 6 months started in December 2020 to July 2021. **Results:** This study enrolled 100 patients with confirmed COVID-19. There was a highly significant variance between severe to critical than in the mild to moderate group about age, male gender, ICU admission, death, CRP, d dimer, ferritin, FBG, and HbA1c as they were higher in severe to critical than in mild to moderate. There was a high statistically significant relation between FBG and Duration of ICU, Ferritin, Smoking, Cholesterol, TG, HDL, LDL, HbA1C, D-dimer, and severity of COVID-19. **Conclusion:** Hyperglycemia was linked to poor outcomes in COVID-19 cases. Baseline hyperglycemia levels were a major predictor for mortality among cases admitted immediately to the ICU.

Keywords: COVID-19; Diabetes; Glucose; Hospital; Mortality.

Introduction

COVID-19 is a viral infection caused by SARS-CoV-2, which increases mortality worldwide. It was initially detected in Wuhan, China, in December 2019 [1].

It began as an epidemic in China, but the WHO finally designated it a global pandemic. Worldwide, on June 29, 2020, there were 10021401 verified instances of COVID-19, with 499913 mortality recorded by WHO [2].

Following the onset of the SARS-CoV-2 epidemic, diabetes was identified as one of the most prevalent comorbidities and a probable driver for negative outcomes. Diabetes mellitus (DM) was more common among COVID-19 cases hospitalized and transferred to the intensive care unit (ICU) or died [3].

A meta-analysis of research investigations reporting case variables based on COVID-19 severity in China indicated that diabetes was associated with a 2-3 fold greater risk of poor illness outcome. These results are consistent with the previous investigations on the unfavorable prognostic effects of DM on other viral illnesses, such as influenza [4].

It is uncertain whether diabetes increases risk irrespective of factors such as comorbidities and complications. Diabetic cases may have had a poorer COVID-19 outcome owing to various organ impairments caused by micro- and macrovascular conditions [5].

New-onset diabetes was recorded throughout COVID-19, however, its influence on the condition's outcome has not been examined [6].

Newly identified diabetes is frequently associated with occult organ impairment, which reduces survival. Furthermore, stress hyperglycemia has been observed for decades to drive an increased inflammatory response in critically ill patients [7].

ACE 2 receptor activation is found not only in the lungs, but also in the epithelium of the esophagus, colon and ileum, and pancreas, cardiovascular and renal organs [8].

ACE 2 messenger RNA concentrations have been determined to be greater in the pancreas than in the lung. This reflects the virus's multi-organ tropism [9].

ACE 2 activity is detected in both the pancreatic acinar part and the endocrine part. The spike protein (S) contacts ACE 2, the entry receptor [10].

This study aims to evaluate the likelihood of developing new-onset DM in COVID-19-infected cases and its possible pathogenesis.

Patients and Methods:

This cross-sectional study was conducted at Ashmoun Fever Hospital and Menouf Fever Hospital, involving 100 patients with confirmed COVID-19 who were admitted and managed in both inpatient wards and isolated ICU departments over a 6-month period, from December 2020 to July 2021. All study procedures adhered to the regulations set by the Benha University Ethical Committee, and informed consent was obtained from all participants. Ethical approval was granted by the Benha Institutional Review Board (IRB) under approval number {M.S.21.8.2021}. The study was carried out under the supervision of the Internal Medicine Department.

The Inclusion Criteria were confirmed cases with COVID-19 infection by PCR (The three most often used criteria in probable case descriptions were fever, difficulty breathing, and proven contact with a possible or confirmed case, patients with various degrees of COVID-19 infection (mild, moderate, and severe). A mild case is characterized as a symptomatic condition with leucopenia or lymphopenia and no radiological signs of pneumonia. Moderate case individual shows pneumonia signs on radiography coupled with symptoms, and/or leucopenia or lymphopenia. Sever case RR > 30 per min, paO2/FiO2 ratio < 300, sa O2 < 92% at room air, chest

radiology showing more than 50% lesion or progressive lesion within 24 to 48 hrs. Critically ill if saO2 > 92 at room air, or RR > 30 per min or paO2/FiO2 ratio < 200 despite O2 therapy, both male and female genders, patients of various ages.

Exclusion Criteria; Patients known to be diabetic, patients with impaired glucose tolerance, patients with a history of gestational diabetes, patients with a family history of diabetes, stress-induced diabetes, any other endocrine disorders that cause secondary diabetes, patients diagnosed with any form of pancreatic disease, patients received medications that raise blood sugar e.g., Steroids, thiazide diuretics, beta-blockers, statins, antipsychotics like clozapine.

All patients were subjected to:

Full history taking including Age, sex, the current condition, its severity, any other associated symptoms were recorded, duration of disease, dialysis duration, previous kidney disease, specific comorbid conditions (e.g., hypertension, cerebrovascular conditions, chronic obstructive pulmonary disease, cancer), smoking, and medications. Thorough clinical examination: Including vital signs and anthropometric measures. Laboratory investigations include CBC, PCR for COVID-19 virus, Serum creatinine, Blood urea, C-reactive protein, D-dimer, Ferritin, Random blood sugar, FBS, PPBS, HbA1c, serum C-peptide, CRP, lipid profile, Urea, Creatinine, protein creatinine ratio, Liver function test (Alanine transaminase, Serum aspartate transaminase, PT., PTT., albumin, bilirubin total and direct, GGT, alkaline phosphatase).

Statistical analysis:

The data was statistically analyzed using the (IBM SPSS for Windows version 22.0, Armonk, NY). Qualitative data were presented in terms of numbers and percentages. The chi-squared (X2) test was utilized to compare qualitative data. Student's t-test was employed to compare quantitative data. Regression analysis is used to classify markers based on their importance in discriminating across distinct patient groups. ANOVA test was utilized to assess statistical significance between three or more means. P-values < 0.05 were significant.

Results:

The study included 100 cases infected with COVID-19.

In **Table 1** there was male predominance as 82% were males and 18% were females. The mean age was 64.43 years.

Table 2 shows the mean fasting glucose was **105.62**± 4.46(mg/dl), the mean HBA1C was **6.38**±1.578%, the mean Post-prandial glucose was 186.78 ± 69.96(mg/dl), the mean cholesterol was 201.20 ± 54.37 (mg/dl), the mean TGs was 197.18 ± 63.87(mg/dl), the mean HDL was **50.32**± 3.67(mg/dl) and the mean LDL was **134.37**± 10.76(mg/dl).

Table 3 shows the most common causes of mortality among diabetic cases with COVID-19 were old age, ICU admission, comorbidity, elevated ICU duration, high D-dimer and ferritin, high FBG, smokers, low O2 saturation, SBP, DBP, high HbA1c.

Table 4 shows there was a high statistically significant relation between FBG and Duration of ICU, Ferritin, Smoking, Cholesterol, TG, HDL, LDL, HbA1C, D-dimer, and Severity of COVID-19.

Table (1): Description of the whole sample

			Count	**%**
Sex		**Female**	18	18%
		Male	82	82%
		Median	**mean**	**Standard deviation**
age	Total	68.57	64.43	5.78
	Male	69.38	66.25	5.24
	Female	64.24	63.13	4.26

Table (2): lipid profiles and glucose metabolism among participants:

		(N=100)
Fasting glucose (mg/dl) Mean ± SD.		**105.62**± 4.46
HBA1C (%) Mean ± SD.		**6.38**±1.578
Post-prandial glucose (mg/dl) Mean ± SD.		186.78 ± 69.96
Cholesterol (mg/dl) Mean ± SD.		201.20 ± 54.37
TGs (mg/dl) Mean ± SD.		197.18 ± 63.87
HDL (mg/dl) Mean ± SD.		**50.32**± 3.67
LDL (mg/dl) Mean ± SD.		**134.37**± 10.76
		(N=100)
Diabetes	**male**	52(52%)
	female	**8(8%)**
Impaired glucose tolerance	**male**	30(30%)
	female	**10(10%)**

N: Number of participants **SD**: Standard Deviation **HbA1c**: Glycated Hemoglobin
HDL: High-Density Lipoprotein **LDL**: Low-Density Lipoprotein **TGs**: Triglycerides

Table (3): Association between clinical data and all causes of mortality among diabetic cases with COVID-19**.**

	Univariate p	OR (95%C.I)
age	0.030*	1.032(1.005 – 1.058)
Male sex	0.863	1.04 (0.64–1.76)
Comorbidity	0.008*	1.146(1.076 – 1.563)
Temperature (° C)	0.273	0.646 (0.296–1.1412)
ICU admission	0.005*	2.40 (1.35–5.79)
Duration of ICU	0.040*	0.664(0.277–1.854)
HGB (gm/dl)	0.444	0.642 (0.36–1.52)
WBCs (103 /cm)	0.439	1.356(0.654–2.471)
Lymphocytes (10^3 /cm)	0.973	0.882 (0.675–1.402)
PLTs (10^3 /cm)	0.279	3.112 (0.389–24.3)
D-dimer(mg/L)	0.009*	1.283 (1.065–1.545)
Ferritin (mic/L)	0.031*	0.503(0.153–1.651)
Iron(mcg/dL)	0.733	21.081(0.142–84.742)
FBG mg/dl	0.037*	2.485 (0.750–8.109)
Urea	0.833	1.250 (0.158–9.895)
Creatinine	0.395	0.719 (0.337–1.536)
Sodium	0.595	1.517 (0.356–7.051)
Potassium	0.085	4.234 (0.820–21853)
Magnesium	0.312	0.887 (0.702–1.120)
Phosphorous	0.330	0.644 (0.207–1.724)
Calcium	0.119	0.341 (0.008–1.318)
PTH	0.067	0.371 (0.130–1.071)
Albumin	0.882	0.973 (0.675–1.402)
Smoking	0.002*	1.001 (1.000–1.000)
O2 saturation	0.046*	8.974 (1.039–77.508)
Systolic BP (mmHg)	0.042*	1.374 (0.775-2.465)
Diastolic BP (mmHg)	0.027*	1.335 (0.735-2.366)
HbA1c	0.035*	0.897 (0.674–1.094)

Table (4): Correlation between FBG mg/dl and different parameters in the studied group**.**

Parameter	FBG mg/dl	
	R	P
Age (years)	0.160	0.478
gender	0.10	0.712
Duration of ICU	0.820	0.004*
Ferritin (mic/L)	0.918	<0.001*
Smoking	0.241	<0.001*
SBP (mmHg)	0.251	0.432
DBP (mmHg)	0.242	0.062
Cholesterol mg/dl	0.995	<0.001*
TG	0.842	<0.001*
HDL	0.970	0.001*
LDL	0.999	0.001*
HbA1C	0.911	0.001*
FBG mg/dl	0.745	0.003*
Post-prandial glucose	0.756	0.002*
D-dimer(mg/L)	0.723	0.000*
Severity of covid	0.838	0.015*
O2 saturation	0.333	0.152

FBG: Fasting Blood Glucose **R**: Correlation coefficient **P**: P-value (statistical significance) **ICU**: Intensive Care Unit **SBP**: Systolic Blood Pressure **DBP**: Diastolic Blood Pressure
TG: Triglycerides **HDL**: High-Density Lipoprotein **LDL**: Low-Density Lipoprotein
HbA1c: Glycated Hemoglobin **D-dimer**: A fibrin degradation product indicating clot formation and breakdown **O_2 saturation**: Oxygen saturation

Discussion:

COVID-19 survivors number hundreds of millions, with some claiming partial recovery months after the initial illness, a phenomenon known as protracted COVID. Cases with extended COVID-19 have several comorbidities [11].

Although the overwhelming evidence that DM is related to worse COVID-19 consequences, there is a scarcity of data on inpatient glycemic management among cases with DM and acute hyperglycemia hospitalized with COVID-19. A direct relationship with healthcare results has not been shown [12]. Previous research has indicated that hyperglycemia on admission to the hospital is predictive of mortality and other serious complications of COVID-19, but whether the treatment that improves glycemia could enhance outcomes has not been investigated by rigorous analysis of postadmission glycemia [13].

The mean aim of the current study was to assess the likelihood of developing new-onset DM in COVID-19-infected cases and its possible pathogenesis. There was male predominance as 82% were males and 18% were females and that coincides with [14] as there were 94.1% of the cases were males. Also**,** [15] showed that most cases were male. Also, in the study done by [16]**,** they found that 88.08% of their studied cases were males. This was [17] stated that males are more susceptible to being diagnosed with COVID-19, particularly beyond the age of 50. The increased incidence in men may be due to higher levels of smoking and drinking among men compared to women.

Regarding HbA1c, the mean HBA1C was 6.38±1.578 and that was near to the results in the study done by [18] the mean HBA1C was 5.79±0.67. Also, in the study done by [16]**,** the mean HBA1C was 5.53±0.35.

According to the mean duration of ICU admission in the present study, it was 9.33 ± 1.46 days while in the study done by [12] It was 6.2± 3.7 days. In another study by [19] who investigated 7337 COVID-19 cases with and without T2DM, and found that those with T2DM needed additional treatments during their hospital stay than

those without DM. It was demonstrated that those with worse blood glucose management had an overall higher death risk than those who had improved management of glucose.

In our study, there was a highly substantial variance between both groups in the severity of COVID-19 as higher CRP was found in severe to critical which disagrees with [20] who found no remarkable variance between the two groups for severe symptoms at admission and CRP. Also, [21] stated that Plasma levels have a positive relationship with COVID-19 severity, and larger levels of CRP were associated with a longer inpatient stay.

In line with the present results, [22] employed US VA data to demonstrate that SARS-CoV-2 was linked with greater risks of onset DM among males but not for females.

There was a highly statistically significant difference between severe to critical than in the mild to moderate group concerning FBG and that coincides with [23] employed VA data to discover that COVID-19 was connected with an elevated risk of T2DM, which was linked with the severity of the disease. In disagreement, [24] demonstrated that cases with a COVID-19 diagnosis had a considerably greater probability of getting new-onset T1DM compared to those without.

As regards sex, there was a non-significant association between male sex and mortality even though 75% of the dead cases were males in line with [25] who found that while there were no significant variances in COVID-19 rates by gender, men had a 20% greater risk of mortality once identified.

In the present report, there was a highly remarkable variance between died than in the survived group as regards duration of ICU and that coincides with [19 and 26] who stated that Improper glucose management predicts a rise in the requirement for drugs, hospitalizations, and mortality.

In the present study, there was a highly statistically significant variance between the dead in surviving group as regards FBG, and that coincides with [13] who reported that mortality was highest in the patients with high FBG. A multicenter retrospective study from China by [27] observed that high fasting glucose levels (≥7.0mmol/l (≥126mg/dl)) upon admission were an independent predictor of higher mortality in COVID-19 cases who did not have DM.

There was a highly significant variance between severe to critical than in the mild to moderate group concerning FBG and that coincides with [28] who showed that cases with DM had more risk of having severe COVID-19 and elevated mortality. Also, [29] revealed that a multi-institutional research network found that severe COVID-19 was linked to a higher risk of new-onset T2D than influenza.

Conclusion:

We conclude that COVID-19 cases with DM and/or unmanaged hyperglycemia spent more time in the ICU and died at a greater rate than those without DM or high blood sugar levels. Hyperglycemia was linked to worse outcomes in COVID-19 cases. Admission hyperglycemia levels were a major predictor of mortality among cases admitted immediately to the ICU. Severe hyperglycemia after admission was a significant predictor of mortality among ICU cases.

References:

1. Kumaran NK, Karmakar BK, Taylor OM. Coronavirus disease-19 (COVID-19) associated with acute necrotising pancreatitis (ANP). BMJ Case Rep. 2020;13:e237903.
2. Lukman AF, Benedicta A, Awotunde JB, Okon CE, Oludoun O, Oluwakemi A, et al. Robust Statistical Modeling of COVID-19 Prevalence in African Epicentres'. In: Azar AT, Hassanien AE, editors. Modeling, Control and Drug Development for COVID-19 Outbreak Prevention [Internet]. Cham: Springer International Publishing; 2022 [cited 2024 Oct 18]. p. 315–58. Available from: https://doi.org/10.1007/978-3-030-72834-2_11
3. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of

diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020;8:546–50.
4. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. J Clin Virol. 2020;127:104354.
5. Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients With Diabetes in Wuhan, China: A Two-Center, Retrospective Study. Diabetes Care. 2020;43:1382–91.
6. Potier L, Julla JB, Roussel R, Boudou P, Gauthier DC, Ketfi C, et al. COVID-19 symptoms masking inaugural ketoacidosis of type 1 diabetes. Diabetes Metab. 2021;47:101162.
7. Davis TME, Coleman RL, Holman RR, UKPDS Group. Prognostic significance of silent myocardial infarction in newly diagnosed type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 79. Circulation. 2013;127:980–7.
8. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Lett. 2002;532:107–10.
9. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. Clin Gastroenterol Hepatol. 2020;18:2128-2130.e2.
10. Muus C, Luecken MD, Eraslan G, Waghray A, Heimberg G, Sikkema L, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells [Internet]. 2020 [cited 2024 Oct 18]. Available from: http://biorxiv.org/lookup/doi/10.1101/2020.04.19.049254
11. Paneni F, Patrono C. Increased risk of incident diabetes in patients with long COVID. Eur Heart J. 2022;43:2094–5.
12. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. J Diabetes Sci Technol. 2020;14:813–21.
13. Klonoff DC, Messler JC, Umpierrez GE, Peng L, Booth R, Crowe J, et al. Association Between Achieving Inpatient Glycemic Control and Clinical Outcomes in Hospitalized Patients With COVID-19: A Multicenter, Retrospective Hospital-Based Analysis. Diabetes Care. 2021;44:578–85.
14. Saris A, Reijnders TDY, Nossent EJ, Schuurman AR, Verhoeff J, Asten S van, et al. Distinct cellular immune profiles in the airways and blood of critically ill patients with COVID-19. Thorax. 2021;76:1010–9.
15. Aisyah DN, Mayadewi CA, Diva H, Kozlakidis Z, Siswanto null, Adisasmito W. A spatial-temporal description of the SARS-CoV-2 infections in Indonesia during the first six months of outbreak. PLoS One. 2020;15:e0243703.
16. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. Lancet Diabetes Endocrinol. 2022;10:311–21.
17. Alsan M, Stantcheva S, Yang D, Cutler D. Disparities in Coronavirus 2019 Reported Incidence, Knowledge, and Behavior Among US Adults. JAMA Netw Open. 2020;3:e2012403.
18. Izzo R, Pacella D, Trimarco V, Manzi MV, Lombardi A, Piccinocchi R, et al. Incidence of type 2 diabetes before and during the COVID-19 pandemic in Naples, Italy: a longitudinal cohort study. EClinicalMedicine. 2023;66:102345.
19. Zhu L, She Z-G, Cheng X, Qin J-J, Zhang X-J, Cai J, 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.e3.
20. Pallotto C, Suardi LR, Esperti S, Tarquini R, Grifoni E, Meini S, et al. Increased CD4/CD8 ratio as a risk factor for critical illness in coronavirus disease 2019 (COVID-19): a retrospective multicentre study. Infect Dis (Lond). 2020;52:675–7.
21. Chen J, Wu C, Wang X, Yu J, Sun Z. The Impact of COVID-19 on Blood Glucose: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2020;11:574541.
22. Wander PL, Lowy E, Beste LA, Tulloch-Palomino L, Korpak A, Peterson AC, et al. The Incidence of Diabetes Among 2,777,768 Veterans With and Without Recent SARS-CoV-2 Infection. Diabetes Care. 2022;45:782–8.
23. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. 2021;594:259–64.
24. Qeadan F, Tingey B, Egbert J, Pezzolesi MG, Burge MR, Peterson KA, et al. The associations between COVID-19 diagnosis, type 1 diabetes, and the risk of diabetic ketoacidosis: A nationwide cohort from the US using the Cerner Real-World Data. Abdelkreem E, editor. PLoS ONE. 2022;17:e0266809.

25. Salerno S, Messana JM, Gremel GW, Dahlerus C, Hirth RA, Han P, et al. COVID-19 Risk Factors and Mortality Outcomes Among Medicare Patients Receiving Long-term Dialysis. JAMA Netw Open. 2021;4:e2135379.
26. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. Diabetes Care. 2018;41:2127–35.
27. Wang S, Ma P, Zhang S, Song S, Wang Z, Ma Y, 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. 2020;63:2102–11.
28. Abdi A, Jalilian M, Sarbarzeh PA, Vlaisavljevic Z. Diabetes and COVID-19: A systematic review on the current evidences. Diabetes Res Clin Pract. 2020;166:108347.
29. Birabaharan M, Kaelber DC, Pettus JH, Smith DM. Risk of new-onset type 2 diabetes in 600 055 people after COVID-19: A cohort study. Diabetes Obes Metab. 2022;24:1176–9.

To cite this article: Medhat A. Khalil , Nabil khattab, Ali E. Ali, Ahmed M. Mostafa, Mohamed A. Mohamed. Correlation of COVID-19 and Development of New Onset Diabetes Mellitus and its Possible Pathogenesis. BMFJ XXX, DOI: 10.21608/bmfj.2025.341658.2273.