International Clinical and Medical Case Reports Journal
Research Article (ISSN: 2832-5788)

Variation in Glycemic Control Post-COVID-19 in Patients with Diabetes Mellitus: A Pilot Study

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Citation: *Manraj Singh Sra, Prayas Sethi, Amulya Gupta, Mehak Arora, Shivam Pandey, Ved Prakash Meena, et al. Variation in Glycemic Control Post-COVID-19 in Patients with Diabetes Mellitus: A Pilot Study. Int Clinc Med Case Rep Jour. 2024;3(12):1-11.*

Received Date: 10 December, 2024**;** **Accepted Date:** 15 December, 2024**;** **Published Date:** 16 December, 2024

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ABSTRACT

Background: Newly diagnosed diabetes mellitus (DM) and worsening of pre-existing DM have been an important consideration during post-COVID care. However, definitive follow-up studies are lacking. We aimed to assess serial changes in glycemic control of patients with DM up to 6 months post-COVID-19 infection in this pilot study.

Methods: Patients with DM, aged ≥18 years with laboratory-confirmed SARS-CoV2 infection were enrolled in this study. The fasting and post-prandial blood glucose levels before COVID-19 infection and 1, 3 and 6 months post-COVID-19 infection were compared.

Results: Among 31 patients completing the follow-up, transient and persistent dysglycemia was seen in 10 (32.2%) and 4 (12.9%) patients, respectively. No significant change was observed in fasting (p=0.845) and post-prandial (p=0.0725) blood glucose levels over 6 months.

Conclusion: No significant changes in glycemic control are observed post-COVID-19 in patients with DM. Transient dysglycemia due to critical illness and corticosteroid use, and withdrawal of insulin during post-COVID-19 follow-up has been observed. Aggressive treatment for glycemic control has also been a factor for better glycemic outcomes and hence no significant overall effect. However, in view of a few patients demonstrating a persistent worsening of glycemic control even in the absence of steroid use or months after use in mild disease, close monitoring of blood sugar is advisable during follow-up. Large-scale studies with robust follow-up may be required in this regard.

Keywords: COVID-19; Diabetes Mellitus; Post-COVID-19 infection; Post-COVID-19 dysglycemia

INTRODUCTION

The mortality of COVID-19 has been disproportionately high in individuals with an advanced age or those having comorbidities like diabetes mellitus, hypertension, cardiovascular diseases, renal disorders, etc. [1] Diabetes mellitus (DM) has been a major comorbidity in patients hospitalized for COVID-19 [2], especially in India, where the prevalence of DM is relatively high. [3] It is proposed that DM leads to worse outcomes in COVID-19 due to a pro-inflammatory state, weakening of the innate immune system, increased ACE2 expression, vascular dysfunction and a prothrombotic state. [4]

Further, it has been proposed that a bidirectional relationship may exist between COVID-19 and Diabetes mellitus such that the infection worsens the glycemic control or causes new-onset DM. [5] Both acute and chronic worsening of glycemic control have been observed in patients of SARS-COV-2 [19]. Even vaccination against SARS-CoV-2 has shown temporal incidents of DKA [20] A Japanese study has also shown that the median HbA1c level of the patients increased significantly from 6.8% before the state of emergency to 7.1% and 7.0% during and after the state of emergency during the pandemic [21]. SARS-CoV2 uses ACE2 receptor to enter cells. During a COVID-19 infection, this may lead to a direct effect on beta cells of the pancreas because of the expression of the ACE2 receptor. [6]. However, some evidence suggests that Neuropilin-1 (NRP-1) plays a major role in facilitating the entry of SARS-CoV2 in the beta cells instead of ACE2 expression.[7] This may lead to impaired insulin secretion by two mechanisms. First, SARS-CoV2 may induce apoptosis of the beta cells and impair insulin production through increased phosphorylation of p21-activated kinase (PAK) and c-Jun N-terminal kinase (JNK). [8] Second, it may induce the trans differentiation of beta cells to glucagon-producing alpha cells or trypsin-producing acinar cells through the Integrated Stress Response (ISR) [9]. Further, COVID-19-induced decrease in the expression of ACE2 may lead to exaggerated Ang II response leading to insulin resistance ACE2 has been thought to have a beneficial effect on DM and decreased ACE2 expression may lead to worsening hyperglycemia [10,11]. In this pilot longitudinal cohort study, we aim to investigate the changes in fasting and post-prandial blood glucose 6 months post-COVID-19 infection in patients with diabetes mellitus.

METHODS

This prospective observational longitudinal cohort study was conducted at a tertiary care hospital from August 2020 to September 2021. Ethical clearance for this study was taken from the institute's ethics committee and informed consent was taken from all participants.

Patient selection

Patients with DM, aged ≥18 years with laboratory-confirmed SARS-CoV2 infection, having a laboratory report of fasting and postprandial blood glucose within 2 months before the onset of COVID-19 symptoms or diagnosis, were included in the study. Patients who were pregnant or taking corticosteroids outside of treatment for COVID-19 were excluded.

Data collection and follow-up

The demographic and medical information was recorded from the hospital database, previous laboratory reports provided by the participants, and telephonic interviews. Fasting and postprandial blood glucose values along with the dose of insulin and/or oral antidiabetic agents were recorded: before COVID-19 infection and 1, 3, and 6 months after COVID-19 infection.

Definitions

The severity of the disease was based on the guidelines of the Ministry of Health & Family Welfare. The mild disease was defined as patients with a respiratory rate (RR) < 24 breaths per minute or oxygen saturation (SpO_2) > 94% on room air. Those with RR between 24 and 30 breaths per minute, or SpO_2 between 90 and 94% on room air were classified as a moderate disease. Patients with RR > 30 breaths per minute or requiring invasive or non-invasive ventilatory support were classified as severe disease. The maximum disease severity during the hospital stay was considered for classifying patients.

Based on the changes in blood glucose levels, patients were classified as experiencing transient dysglycemia (early or late) or persistent dysglycemia. Transient dysglycemia was defined as an increase in fasting blood glucose by >29 mg/dl (approximately an increase of 1% HbA_{1c}) as compared to the immediately previously recorded blood glucose levels which subsequently decreased with or without modification of medications.[12] Patients experiencing transient dysglycemia at the 1-month or the 3- or 6-month follow-up post-COVID-19 infection were termed to be experiencing early or late transient dysglycemia, respectively. Persistent dysglycemia was defined as an increase in fasting blood glucose by >29mg/dl as compared to the immediately previous recorded blood glucose level which persisted at 2 or more follow-ups.

Statistical Analysis

Only patients with records of fasting and post-prandial blood glucose at all four-time points were included in the final analysis. Continuous variables were checked for normality using the Shapiro-Wilk test. Fisher's exact test and the Kruskal-Wallis test were used to compare categorical and continuous variables, respectively. Mauchly's test was used to examine the sphericity of recorded blood glucose levels. Differences in blood glucose levels at different time points were analyzed using the Friedman test. Pairwise comparisons of blood glucose levels at different time points were done using the Wilcoxon signed-rank test and Bonferroni correction was applied. All statistical analysis was done in R.

RESULTS

A total of 49 patients were enrolled, of which data of 31 were analyzed. 19, 8 and 4 patients were followed up in the mild, moderate and severe disease group. Detailed patient characteristics are shown in Table I. Hypertension was the most common comorbidity seen in 23 (74.19 % patients) All included in the final analysis completed 6 months of follow-up. The last recorded fasting blood sugar levels (pre-COVID-19) were 123, 129.5 and 169 mg/dl in mild, moderate and severe disease respectively and that of post-prandial blood sugar were 200, 197.5 and 221.5 mg/dl respectively.

Overall, 17 (54.84%) patients saw either an improvement in fasting blood glucose levels or an increase of less than 29 mg/dl during 6 months. Early and late transient dysglycemia was seen in 4 (12.90%) and 6 (19.35%) patients, respectively. Prolonged dysglycemia was seen in 4 (12.90%) patients, all being mild disease. 3 patients

had transient hyperglycemia in the mild disease, which was improved by adding extra anti-diabetic medications. Changes in glycemic status stratified by COVID-19 infection severity are summarized in Figure 1.

The fasting blood glucose levels at different time points were not statistically different for the entire cohort (p = 0.845) and subgroups of mild (p=0.932), moderate (p=0.352) and severe (p=0.589) disease. In patients with mild disease, there was an overall increase in median fasting blood sugar levels from 123 mg/dl pre-COVID-19 to 130 mg/dl post-COVID-19 first month [Table II, Figure 2 (A)]. Similarly, no statistically significant differences were observed in the post-prandial blood glucose levels at different time points for the entire cohort (p = 0.0725) and subgroups of mild (p = 0.0681), moderate (p=0.537), and severe (p = 0.0741) disease. In patients with mild disease, there was an overall increase in median post-prandial blood sugar levels from 200 mg/dl pre-COVID-19 to 213 mg/dl post-COVID-19 first month [Table III, Figure 2 (B)], Pairwise comparisons between different time points did not reveal any statistically significant differences in both fasting and post-prandial blood glucose levels for the entire cohort and the sub-groups.

Of the 4 patients who had shown persistent hyperglycemia, 1 patient had increased use of anti-diabetic medications whereas the other 3 patients continued to be on the same treatment for diabetes. The trajectory of the fasting and post-prandial blood glucose of these patients is shown in Figure 3.

Table I: Characteristics of study participants with complete follow-up

Parameter	All participants (n=31)	Mild Disease (n=19)	Moderate Disease (n=8)	Severe Disease (n=4)	p-value
Age in years [median(IQR)]	50 (46-65)	50 (46-65)	54.5 (47-57.5)	43.5 (38.5-65)	0.4614
Male gender	23 (74.19)	15 (78.95)	5 (62.50)	3 (75.00)	0.835
Comorbidities other than DM					
Hypertension	23 (74.19)	13 (68.42)	7 (87.5)	3 (75)	0.948
Coronary artery disease	5 (16.12)	3 (15.79)	1 (12.5)	2 (50)	
Hypothyroidism	4 (12.90)	2 (10.53)	1 (12.5)	1 (25)	
Post-renal transplantation	2 (6.45)	0 (0)	1 (12.5)	1 (25)	
Peripheral artery disease	1 (3.22)	1 (5.26)	0 (0)	0 (0)	
Cerebrovascular accident	1 (3.22)	1 (5.26)	0 (0)	0 (0)	
Pancreatitis	1 (3.22)	1 (5.26)	0 (0)	0 (0)	
Lymphoma	1 (3.22)	1 (5.26)	0 (0)	0 (0)	

Data are shown as count (percentage) unless otherwise specified. DM: Diabetes Mellitus; IQR: Inter-quartile range.

Table II: Fasting blood glucose levels at different time points

Group	Pre-COVID-19	Post-COVID-19 (1 month)	Post-COVID-19 (3 months)	Post-COVID-19 (6 months)	p-value
All Patients	126	129	130	123	0.845
	(110-174)	(115-148)	(110-142)	(110-140)	
Mild Disease	123	130	120	123	0.932
	(110-140)	(117-160)	(106-145)	(108-140)	
Moderate	129.5	115	120	120	0.352

Disease	(94.5-178.5)	(104.25-144.75)	(108-141.5)	(97.25-130)	
Severe Disease	169	120.5	140	130	0.589
	(114-237.5)	(90-187.75)	(140-180.5)	(114-155)	

Data is shown as median (inter-quartile range).

Table III: Post-prandial blood glucose at different time points

Group	Pre-COVID-19	Post-COVID-19 (1 month)	Post-COVID-19 (3 months)	Post-COVID-19 (6 months)	p-value
All Patients	200	185	170	160	0.0725
	(166.5-250)	(157.25-226.25)	(145-209)	(140-190)	
Mild Disease	200	213	170	170	0.0681
	(169.5-242.5)	(163.5-245)	(151.9-206.5)	(145-208)	
Moderate Disease	197.5	162.5	150	140	0.537
	(146.25-307)	(147.5-179.75)	(130-210)	(130-160)	
Severe Disease	221.5	182	200	160	0.0741
	(174-327.5)	(163.25-200)	(145-244)	(140-180)	

Data is shown as median (inter-quartile range).

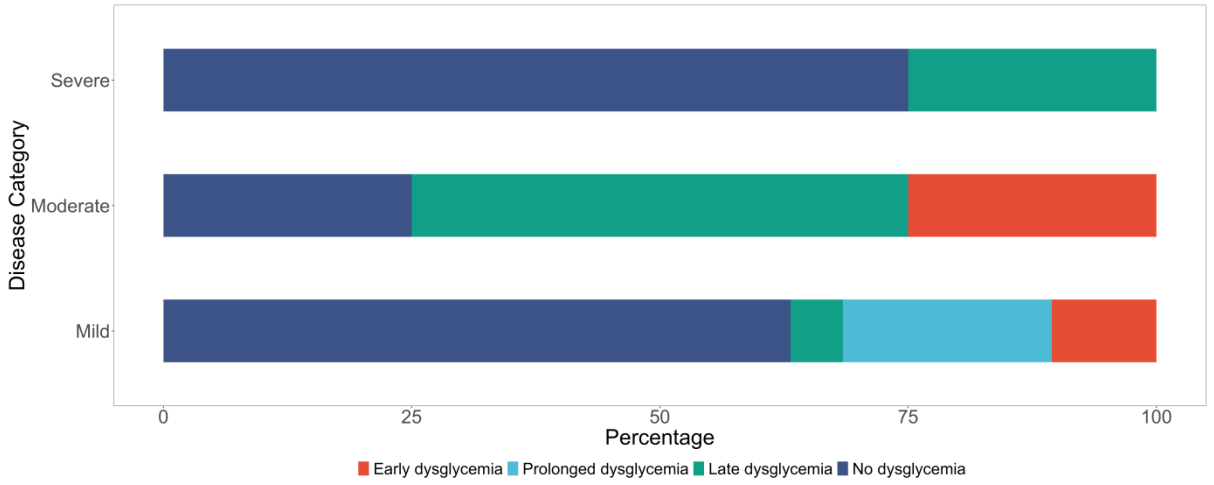

Figure 1: Glycemic outcomes in patients with mild, moderate, and severe disease.

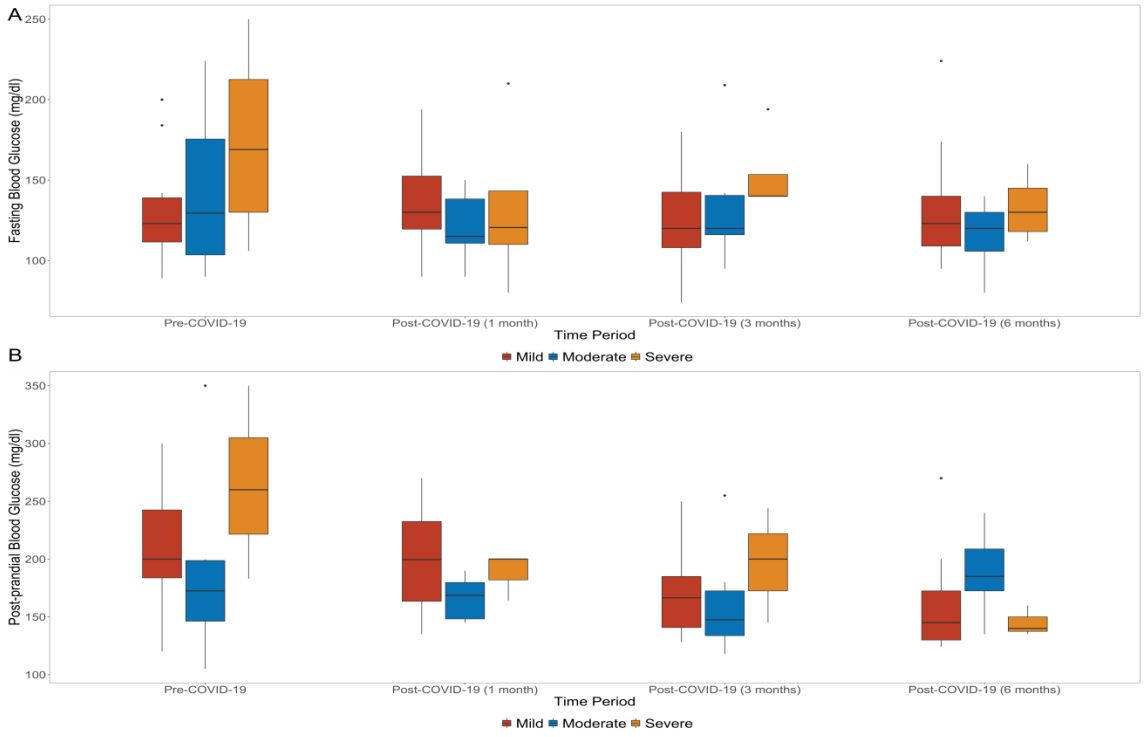

Figure 2: Changes in fasting (A) and post-prandial (B) blood glucose levels in patients with mild, moderate, and severe disease.

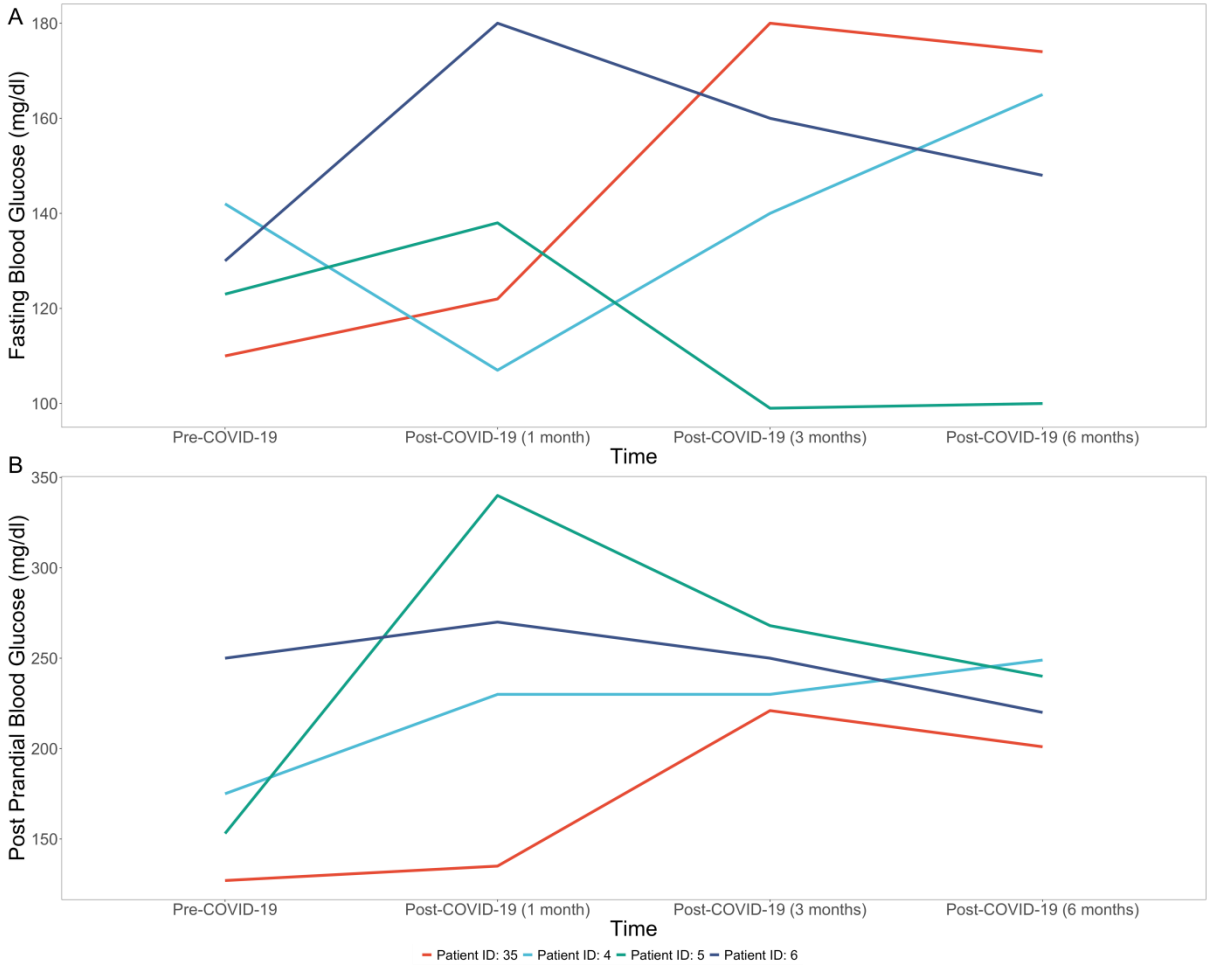

Figure 3: (A) Fasting and (B) post-prandial blood glucose trajectory in patients with persistent dysglycemia.

DISCUSSION

Overall, we observed no significant changes in the fasting and post-prandial blood glucose up to 6 months post-COVID-19 infection among patients with a prior diagnosis of DM. Another longitudinal study observed that there is no significant change in the glycemic and insulin indices, despite progression in body mass index categories [13]. The transient dysglycemia observed in moderate and severe disease groups can be explained by the critical illness, corticosteroid use during illness, and subsequently, withdrawal of insulin therapy post-COVID-19 infection [14–17]. Since there were changes in medications to reach target blood sugars during follow-up, especially in moderate and severe disease patients requiring hospitalization and mild disease patients with high blood glucose, it is difficult to ascertain the extent of variation in glycemic control due to COVID-19. However, since mild disease patients neither received steroids nor were they critically ill enough to have stress, glycemic changes are less likely to happen. So, any variation in the mean blood glucose values is likely due to the disease itself and merits attention. In our study, an increase in fasting and post-prandial blood sugar in mild disease in the first month was noteworthy because these patients were otherwise not critically ill and hence, disease per se may be responsible for an increase in the levels. A later decrease may be due to regular follow-up and alteration of medication. In our study, four patients with mild disease were found to have persistent

hyperglycemia with medication escalation in 1 patient. This highlights the need for a rigorous follow-up after the resolution of infection even in mild cases.[18] To conclude, this pilot study suggests that COVID-19 doesn't significantly perturb glucose control but it is important to monitor blood glucose post-COVID-19 as isolated cases may show glycemic excursions and need for escalation of anti-diabetic drugs.

The key strength of our study was a comprehensive longitudinal follow-up and the correlation of variations of glycemic status with COVID-19 infection severity. The major limitation was the small sample size and since treatment was escalated in a few patients with mild disease, definitive values of blood sugar may not be reliable. Larger, well-designed studies will be required to provide definitive recommendations and factors affecting the glycemic status.

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Supplementary Table I: Characteristics of patients completing follow-up and patients lost to follow up

Parameter	Completed follow up (n=31)	Lost to follow up (n=18)	p-value
Age in years [median (IQR)]	52 (46-65)	56 (44.5 – 60.5)	0.819
Males	23 (74.19)	8 (44.44)	0.122
Comorbidities			
Hypertension	23 (74.19)	5 (27.78)	0.015
Coronary Artery Disease	6 (19.35)	2 (11.11)	
Hypothyroidism	4 (12.9)	0 (0)	
Lymphoma	1 (3.23)	0 (0)	
Cerebrovascular accident	1 (3.23)	0 (0)	
Pancreatitis	1 (3.23)	0 (0)	
Post-renal transplant	2 (6.45)	0 (0)	
Chronic Kidney Disease	1 (3.23)	0 (0)	
Peripheral Artery Disease	1 (3.23)	0 (0)	
Disease Severity			
Mild	19 (61.29)	7 (36.84)	0.059
Moderate	8 (25.81)	3 (15.79)	
Severe	4 (12.9)	8 (42.11)	

Data is shown as count (percentage) unless otherwise specified. IQR: Inter-quartile range.