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Brief Report

Glycemia and New-Onset Diabetes among COVID-19 Patients with Prediabetes: A Follow-Study of Case Series in India

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Abstract: Studies have shown that COVID-19 patients with prediabetes frequently present with high plasma glucose levels on hospital admission. However, whether the glycemic abnormalities are temporary or persist after recovery from the illness is unclear. We conducted a follow-up study of the case series of 69 COVID-19 patients with prediabetes (HbA1c 5.7–6.4%) who were admitted to a tertiary care hospital in Chennai, India, from May to October 2020 and were discharged alive. Over a mean follow-up of 146.6 (SD: 72.5) days, the mean fasting plasma glucose rose significantly by 16.8 mg/dL (from 119.3–136.1 mg/dL), 2-hr post-prandial glucose by 61.0 mg/dL (from 176.2–237.2 mg/dL), and HbA1c by 0.6% (5.9–6.5%). Of the 49 (84.5%) patients who were discharged with glucose-lowering medications, 40 (81.6%) continued taking them at the first follow-up visit (mean of 50.1 days from admission), and 39 (79.6%) continued taking them at the second follow-up visit (mean of 114.3 days from the first follow-up visit). In addition, 12.1% of patients developed new-onset diabetes after recovery from the illness. These findings underscore the importance of regular monitoring of glycemic parameters in COVID-19 patients with prediabetes after recovery.

Keywords: coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); prediabetes; new-onset diabetes; diabetes; HbA1c; long COVID

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1. Introduction

Coronavirus disease 2019 (COVID-19) has caused substantial damage to global health and the economy. According to the World Health Organization, as of 11 November 2022, there have been 631 million confirmed COVID-19 cases globally, including 6.6 million deaths [1]. Research shows that this infectious disease pandemic is lethally intersecting with the ongoing non-communicable disease pandemic, namely diabetes [2]. On the one hand, diabetes worsens the clinical course of COVID-19 patients, with meta-analyzed relative risks ranging between 2.06 and 2.79 for severe illness and 1.75 and 3.21 for mortality, compared to those without diabetes [2]. Multiple factors likely contribute to the risk of worse outcomes in COVID-19 patients with diabetes, including older age, male sex, non-white ethnicity, comorbidities (e.g., hypertension), obesity, and a pro-inflammatory and pro-coagulative state [2]. On the other hand, COVID-19 may induce new-onset diabetes [3,4], with meta-analyses showing relative risks ranging between 59% and 66% compared to those without COVID-19 [5–9]. Most new-onset diabetes cases in the studies included in these meta-analyses were type 2 [5–9]. Potential mechanisms explaining the occurrence of new-onset diabetes after COVID-19 include, but are not limited to, direct or indirect (by triggering cytokines or enhancing autoimmunity) cytolytic effects of the virus on β-cells, activation of the hypothalamic–pituitary–adrenal and sympathoadrenal axes causing an increase in counterregulatory hormones, activation of the renin–angiotensin system resulting in unopposed deleterious actions of angiotensin II, increased surveillance and

screening, use of steroids for treatment, and reduced physical activity and access to healthy foods due to lockdown and quarantine measures [10].

One of the predisposing factors for COVID-19 patients to develop new-onset diabetes and experience severe illness is prediabetes [11,12]. While studies have shown that COVID-19 patients with prediabetes (HbA1c 5.7–6.4%) frequently present with high levels of plasma glucose on hospital admission [11,12], it is unclear whether these high levels are temporary or persist after recovery from the illness. It is important to determine this so that measures can be taken to prevent the development of diabetes, if needed. Therefore, we aimed to study the levels of glycemia and the incidence of new-onset diabetes in COVID-19 patients with prediabetes after they were discharged from a tertiary care setting in India.

2. Materials and Methods

2.1. Study Design, Setting, and Selection of Participants

Figure 1 shows the recruitment and follow-up of patients for the study. We recruited all 102 COVID-19 patients with prediabetes (aged $\geq$ 18 years) who were admitted to a tertiary care hospital in Chennai, India, between May and October 2020. Of these 102 patients, 33 (32.4%) died in the hospital, and the remaining 69 (67.6%) were discharged alive after recovery. We conducted phone calls to invite these 69 patients to the study center for a monthly follow-up visit. Of the cohort of 69 patients, 58 (84.1%) attended both follow-up visits, while the rest 11 (15.9%) were lost to follow-up: 3 died before the first follow-up visit, 2 were unwilling to participate, 3 did not have time to participate, and 3 were unreachable. The diagnosis of COVID-19 was made by a positive reverse transcription polymerase chain reaction (RT-PCR) test, or chest computed tomography (CT) findings and/or clinical signs and symptoms consistent with COVID-19 infection. Prediabetes was defined as an HbA1c of 5.7–6.4%, as per the American Diabetes Association criteria [13], with no previous history of diabetes.

2.2. Data Collection on Hospital Admission

At the time of hospital admission, from the case report forms, we extracted data on the patient's demographics, clinical signs and symptoms, comorbid conditions, physical measurements, laboratory parameters, RT-PCR results, CT findings, medications, and other treatment strategies, complications, and clinical outcomes. RT-PCR, blood tests, and chest CT were performed within 24 h to three days of hospital admission.

2.3. Follow-Up Visits

During follow-up visits, we collected blood samples for fasting and post-prandial glucose and HbA1c and recorded the history of oral hypoglycemics and insulin usage. Self-reports of taking glucose-lowering medications were cross-checked with the medications the patients brought during the visits.

2.4. Plasma Glucose and HbA1c Analysis

Venous blood samples were drawn in a fasting state (fasted for at least eight hours) and two hours after food intake. The blood samples were processed on a COBAS 6000 analyzer for plasma glucose (using Hexokinase assay) and on a D-10 BIORAD analyzer (Hercules, CA, USA) for HbA1c (using High-Performance Liquid Chromatography method), with kits supplied by Roche diagnostics, Basel, Switzerland, in a laboratory accredited by the National Accreditation Board for Testing and Calibration Laboratories (NABL) [14].

2.5. Definition of New-Onset Diabetes

New-onset diabetes during follow-up was defined as fasting plasma glucose (FPG) $\geq$ 126 mg/dL or 2-hr post-prandial glucose $\geq$ 200 mg/dL or taking glucose-lowering medications with HbA1c < 6.5% [7].

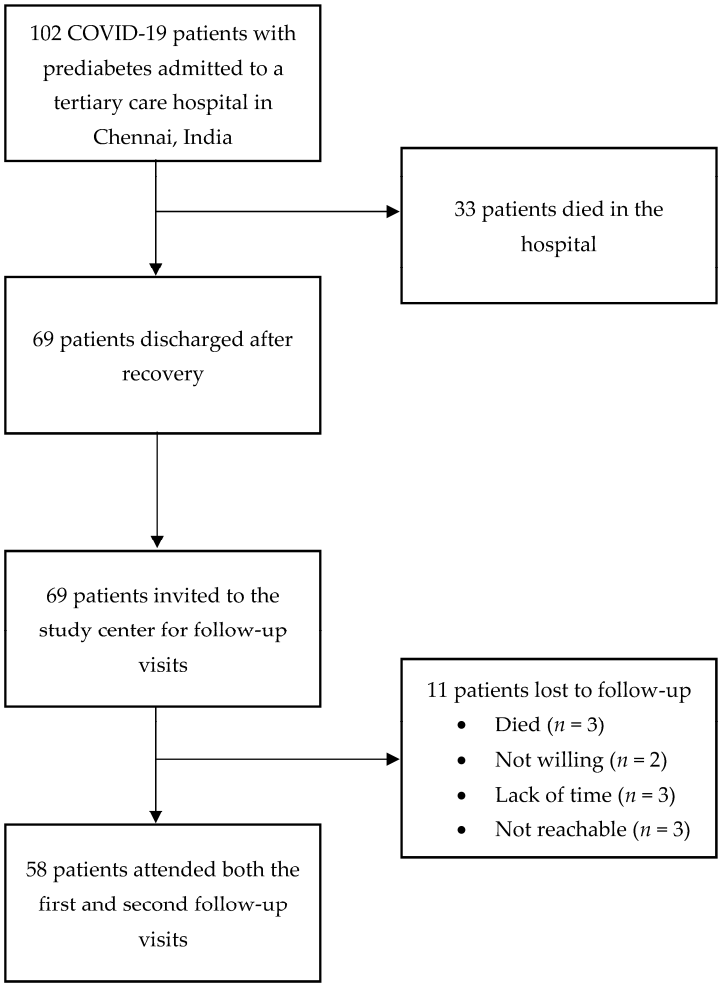

Figure 1. Recruitment and follow-up of COVID-19 patients with prediabetes.

2.6. Statistical Analysis

Continuous variables are summarized with mean (standard deviation, SD) or median (inter-quartile range, IQR) and categorical variables with *n* (%). Mixed-effects linear regression with the maximum likelihood estimation method [15] was used to assess the changes in FPG and 2-hr post-prandial glucose from baseline to follow-up visits. Timepoint (baseline and follow-up visits) was specified as a fixed effect, and a random effect was specified for patients to account for the correlation between the repeated measurements taken from the same patient. A two-sided $p < 0.05$ was considered to be statistically significant. Analyses were performed using Stata version 17.0 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Characteristics of Patients on Admission

Table 1 shows the characteristics of the cohort of 69 COVID-19 patients with prediabetes on hospital admission. The mean age was 44.9 (SD: 13.6) years, and the majority (71%) were male. Most (62.3%) patients had a severe or critical illness, while the rest (37.7%) had a moderate illness, as defined by the World Health Organization criteria [16]. Nearly two-thirds (65.2%) had a history of one or more comorbidities, such as hypertension, chronic kidney disease, coronary heart disease, chronic liver disease, and cerebrovascular accident. A substantial proportion of patients had high levels of certain inflammatory and coagulation indices. For example, one-third (33%) of patients had D-dimer levels of ≥250 ng/mL (considered high), and 58% had a longer prothrombin time of >13.5 s. Additionally, 61% developed one or more complications, including acute respiratory distress syndrome, septic shock, thrombosis, and acute kidney injury.

Table 1. Characteristics of the cohort of 69 COVID-19 patients with prediabetes on hospital admission.

Symptoms, *n* (%)		**Demographics, Mean (SD) or *n* (%)**	
Feve	53 (76.8)	Age (years)	44.9 (13.6)
Fatigue	56 (81.2)	Male	49 (71.0)
Cough	42 (60.9)	**Behavioral factors, *n* (%)**	
Sputum	31 (44.9)	Smoking	35 (50.7)
Sore throat	52 (75.4)	Alcohol use	33 (47.8)
Running nose	27 (39.1)	**Comorbidities, *n* (%)**	
Odynophagia	22 (31.9)	Hypertension	34 (49.3)
Headache	39 (56.5)	Chronic kidney disease	5 (7.3)
Dizziness	31 (44.9)	Coronary heart disease	4 (5.8)
Chest pain	10 (14.5)	Chronic liver disease	4 (5.8)
Chest tightness	23 (33.3)	Cerebrovascular accident	5 (7.4)
Dyspnea	41 (59.4)	One or more comorbidities	45 (65.2)
Nausea	13 (18.8)	**Clinical parameters, mean (SD) or *n* (%)**	
Vomiting	12 (17.4)	Positive RT-PCR	62 (89.9)
Diarrhea	11 (15.9)	Chest CT imaging—area of lung injury $\leq$50% >50%	 62 (89.9) 7 (10.1)
Abdominal discomfort	15 (21.7)	Body mass index (kg/m^2)	26.9 (4.3)
Loss of smell	32 (46.4)	Systolic blood pressure (mmHg)	124.6 (16.0)
Loss of taste	32 (46.4)	Diastolic blood pressure (mmHg)	78.5 (10.8)
Loss of appetite	34 (49.3)	**Blood cells, mean (SD) or median (IQR)**	
Sleep disturbances	22 (31.9)	Total leucocyte count (cells per mm^3)	6600 (5200–10,000)

Table 1. *Cont.*

Symptoms, *n* (%)		**Demographics, Mean (SD) or *n* (%)**	
Palpitation	24 (34.8)	Neutrophil count (cells per mm^3)	4092 (2880–7138)
Vital signs, mean (SD)		Lymphocyte count (cells per mm^3)	1504 (948–2226)
Pulse rate (beats/min)	86.9 (12.6)	Neutrophil-to-lymphocyte ratio	2.6 (1.7–7.2)
Respiratory rate (beats/min)	22.0 (4.4)	Platelet count (cells per mm^3)	240,000 (190,000–284,000)
Sp02 (%)	99.6 (3.0)	Urea (mg/dL)	11 (8–14)
Inflammatory markets and coagulation indices, mean (SD) or median (IQR)		Creatinine (mg/dL)	0.8 (0.7–1.0)
D-dimer (ng/mL)	222 (183–280)	eGFR (mL/min/1.73 m^2)	95.9 (32.2)
Ferritin (ng/mL)	192 (104–305)	Total bilirubin (mg/dL)	1.0 (0.9–1.2)
C-reactive protein (mg/L)	40 (16.4–104)	Total protein (g/dL)	6.7 (0.5)
Interleukin-6 (pg/mL)	12 (6–22)	Albumin (g/dL)	3.7 (0.5)
Prothrombin time (in seconds)	14 (12–16)	Globulin (g/dL)	3.0 (0.5)
aPTT (in seconds)	28.5 (6.3)	Alanine aminotransferase (U/L)	32 (22–45)
International normalized ratio	1.13 (0.13)	Aspartate aminotransferase (U/L)	40 (28–61)
Glucose parameters, mean (SD)		**Lipids, mean (SD)**	
Fasting plasma glucose (mg/dL)	119.3 (21.1)	Total cholesterol (mg/dL)	236.0 (61.8)
2 hr post-prandial glucose (mg/dL)	176.2 (34.9)	Triglycerides (mg/dL)	154.7 (43.5)
HbA1c (%)	5.9 (0.2)	HDL cholesterol (mg/dL)	39.0 (5.8)

SD—standard deviation; IQR—inter-quartile range. aPTT—activated partial thromboplastin time; eGFR—estimated glomerular filtration rate; RT-PCR—reverse transcription polymerase chain reaction.

About 69% received steroids (Dexamethasone) along with antivirals (Table 2). The mean FPG (119.3 mg/dL) and 2-hr post-prandial glucose (176.2 mg/dL) were in the prediabetes range. In total, 84.5% of patients were discharged with oral hypoglycemics (metformin or glimepiride) or insulin (Table 2).

Table 2. Treatment, complications, and clinical outcomes of the cohort of 69 COVID-19 patients with prediabetes.

In-Hospital Treatment, *n* (%)	
Favipiravir	69 (100)
Remdesivir	42 (60.9)
Dexamethasone	69 (100)
Ceftriaxone	16 (23.2)
Low molecular weight heparin	69 (100)
Supplemental oxygen (non-invasive)	33 (47.8)
Mechanical ventilation	16 (23.2)
Complications, *n* (%)	
Acute respiratory distress syndrome	28 (40.6)
Septic shock	15 (21.7)
Thrombosis	5 (7.3)
Acute kidney injury	8 (11.6)
Intensive care unit admission	16 (23.2)
Clinical outcomes, mean (SD)	
No. of hospital days	9.0 (4.1)

SD—standard deviation.

3.2. Longitudinal Changes in Glycemic Parameters

Figure 2 and Table 3 show the changes in glycemic levels from the time of hospital admission to follow-up visits. The mean duration of follow-up of patients was 146.6 (SD: 72.5) days. After a slight non-significant reduction in the mean FPG from 119.3 (SD: 21.1) mg/dL on hospital admission to 116.3 mg/dL at the first follow-up visit ($p = 0.62$), it rose significantly to 136.1 mg/dL at the second follow-up visit ($p = 0.005$). On the other hand, the mean 2-hr post-prandial glucose continuously increased from 176.2 mg/dl at the time of hospital admission to 195.5 mg/dL at the first follow-up visit ($p = 0.019$) and 237.2 mg/dL ($p < 0.001$) at the second follow-up visit. HbA1c increased from 5.9% to 6.4% ($p < 0.001$) and 6.5% ($p < 0.001$) at the first and second follow-up visits, respectively.

3.3. Glucose-Lowering Medications and New-Onset Diabetes

Of the 49 (84.5%) patients who were discharged with glucose-lowering medications, 40 (81.6%) continued taking them at the first follow-up visit (mean of 50.1 days from admission), and 39 (79.6%) continued taking them at the second follow-up visit (mean of 114.3 days from first the follow-up visit). In addition, two patients started taking glucose-lowering medications, as advised by their treating physicians, for the first time during follow-up. New-onset diabetes was detected among 7 (12.1%) patients during follow-up.

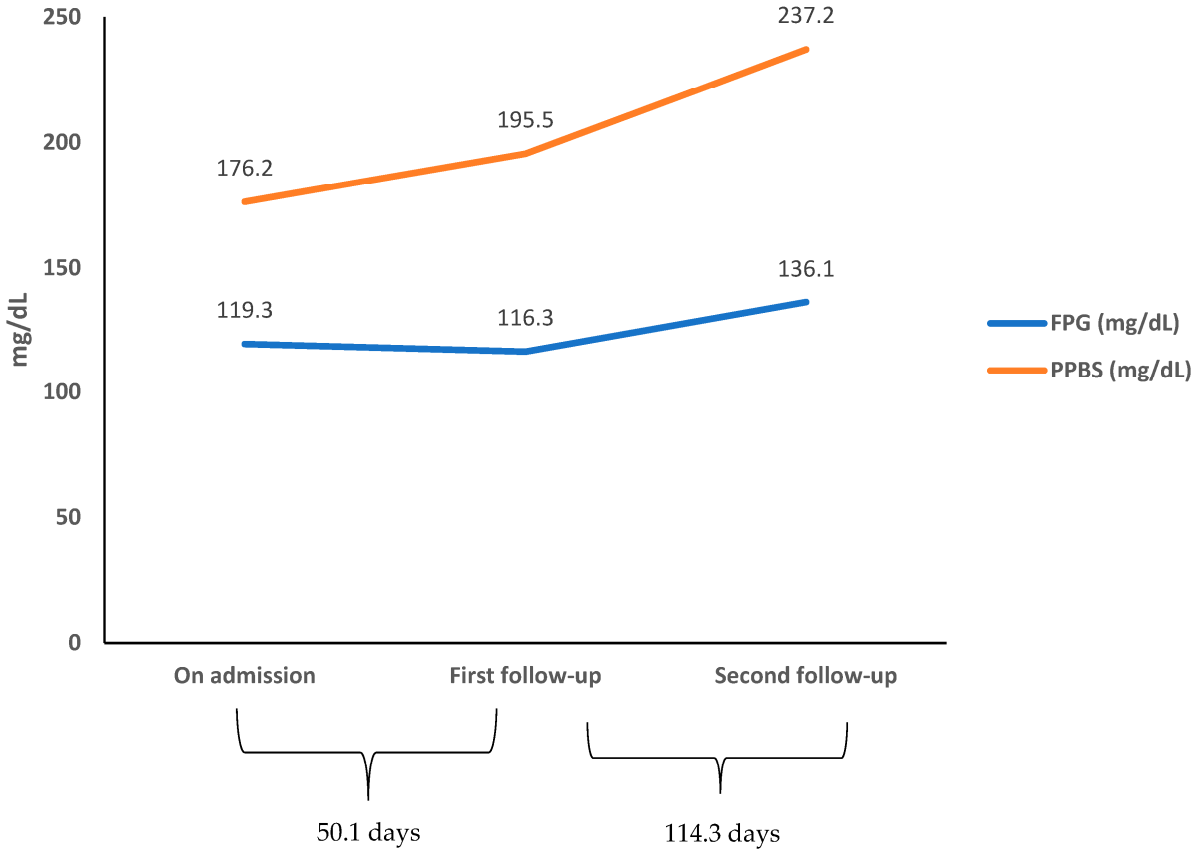

Figure 2. Changes in glucose levels from hospital admission to first and second follow-up visits. FPG—fasting plasma glucose; PPBS—post-prandial blood sugar.

Table 3. Changes in glycemic parameters between baseline and follow-up visits.

	N	First Follow-Up (Mean (SD))	Mean Change from Baseline (95% CI)	*p*	N	Second Follow-Up (Mean (SD))	Mean Change from Baseline (95% CI)	*p*
FPG (mg/dL)	58	116.3 (37.1)	−3.0 (−14.7 to 8.7)	0.62	58	136.1 (46.4)	16.8 (5.1 to 28.5)	0.005
PPBS (mg/dL)	58	195.5 (61.6)	19.3 (3.1 to 35.5)	0.019	58	237.2 (61.0)	61.0 (44.8 to 77.2)	<0.001
HbA1c (%)	58	6.4 (0.8)	0.5 (0.4 to 0.7)	<0.001	58	6.5 (0.7)	0.6 (0.4 to 0.7)	<0.001

SD—standard deviation; FPG—fasting plasma glucose; PPBS—post-prandial blood sugar; CI—confidence interval. Baseline refers to the time of hospital admission. *p* values were derived from the mixed-effects linear regression models, adjusting for baseline values.

4. Discussion

To the best of our knowledge, this is the first study from India to provide data on longitudinal changes in glycemic parameters among COVID-19 patients with prediabetes. Over a mean of five months of follow-up, the mean FPG rose significantly by 16.8 mg/dL (95% CI 5.1 to 28.5 mg/dL), 2-hr post-prandial glucose by 61.0 mg/dL (95% CI 44.8 to 77.2 mg/dL), and HbA1c by 0.6% (95% CI 0.4 to 0.7%). These changes occurred even though a substantial proportion (around 80%) of patients were taking glucose-lowering medications at discharge and during follow-up. Finally, 12.1% of patients developed new-onset diabetes after recovery from the illness.

Prediabetes is an intermediate stage between normoglycemia and diabetes, which is characterized by chronic low-grade inflammation, impaired innate immunity, poor adap-

tive immune response to infections, and a pro-coagulative state [17]. Therefore, people with prediabetes are prone to developing cytokine storm when infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19 [18]. In agreement with this, a significant percentage of our patients had high levels of certain inflammatory markers (e.g., D-dimer) and coagulation indices (e.g., prothrombin time) on admission, possibly resulting in increased insulin resistance [2]. Further, studies have shown that SARS-CoV-2 infects pancreatic ß-cells and possibly reduces insulin secretion [2,10]. These metabolic abnormalities (impaired ß-cell function and insulin resistance) have been shown to persist for several months after recovery [19], which may have contributed to the continued increase in glucose and HbA1c levels among our patients during follow-up. In addition, the indirect effects of COVID-19 on metabolic health (e.g., reduced physical activity due to lockdown), use of corticosteroids during hospitalization, or inadequate dosage and/or poor adherence to medications could also have played a role.

One interesting observation is that the mean FPG increased by 14% (16.8/119 mg/dL), greater than a 10% (0.6/5.9%) increase in mean HbA1c levels. As discussed above, the metabolic abnormalities caused by SARS-CoV-2 infection can persist for several months after recovery, particularly in those who had critical illness [19]. The majority (62.3%) of our study patients were critically ill at admission. HbA1c levels are not affected by critical illness, unlike glucose levels [20,21]. Thus, it is possible that the persistence of SARS-CoV-2-induced metabolic abnormalities in the post-COVID phase could have influenced the fasting glucose levels to a greater extent than the HbA1c levels.

Another important finding is that 12.1% of our patients developed new-onset diabetes during follow-up. This is similar to the finding from a meta-analysis of eight studies of 3711 hospitalized COVID-19 patients, which reported that 14.4% had new-onset diabetes [3]. Several mechanisms may contribute to the development of diabetes following COVID-19, including direct and indirect (by triggering pro-inflammatory cytokines or by enhancing autoimmunity) injury to the ß-cells by SARS-CoV-2, cytokines-induced insulin resistance, disruption of the renin–angiotensin system, and unhealthy behavioral changes due to lockdown and other pandemic control measures [11].

The study has certain limitations. First, we studied only patients with moderate to critical illness admitted to the special wards of the hospital, missing out on those with the mild disease treated in the general wards, thereby resulting in a selection bias. Prediabetes was defined using HbA1c values alone. We could have identified more eligible patients if we had used glucose values, too. Our study was conducted in a single tertiary care setting, with the majority of patients having a severe or critical illness, which limited the generalizability of the findings to those with mild illness not requiring hospitalization. Finally, while we had a high follow-up rate (88%) at both visits, the mean follow-up was only five months. Further follow-up of these patients is needed to study the changes in glycemic parameters over a more extended period of time.

5. Conclusions

In this case series of COVID-19 patients with prediabetes, the mean fasting, 2-hr postprandial glucose, and HbA1c levels increased significantly over a mean follow-up of five months, reaching the diabetes range. These findings emphasize the need for regular monitoring of glucose and HbA1c levels in COVID-19 patients with prediabetes after recovery.

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Institutional Review Board Statement: The study was approved by the Institutional Review Board of the Chettinad Hospital and Research Institute, Tamil Nadu, India (191/IHEC/Nov2020).

Informed Consent Statement: Patient consent on hospital admission was waived by the Institutional Review Board, given the acute nature of the patients' illness. Written informed consent was obtained from all patients at follow-up visits.

Data Availability Statement: The data is available from the senior author upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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