Original Article

Long-term outcome of patients with diabetic-range hyperglycemia first detected during admission for COVID-19: A single-center observational study

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Abstract

Background and Objective: Diabetic-range hyperglycemia has been reported for the first time in many patients during their hospitalization with coronavirus disease 2019 (COVID-19). This study was undertaken to determine the proportion of such patients who actually have new-onset diabetes mellitus rather than transient hyperglycemia during acute illness. **Methods:** This descriptive study included patients with diabetic-range hyperglycemia first detected at or during admission for COVID-19 but no prior history of diabetes. The study protocol involved patient identification, data recording from the case-notes, and telephonic follow-ups. Blood sugar levels done at least two weeks after discharge or the last dose of steroids, whichever was later, were recorded, and patients were categorized as diabetic, pre-diabetic, or non-diabetic accordingly. **Results:** Out of 86 patients, ten (11.6%) were found to have developed diabetes, and 13 (15.1%) had pre-diabetes on follow-up. About 63 (73.3%) patients had become normoglycemic. Eight (80%) out of the ten patients with new-onset diabetes were on treatment, with five (50%) achieving the target glycemic levels. The associations of new-onset diabetes with age, gender, comorbidities, intensive care stay, and steroid administration were not found to be statistically significant (*p*-values 0.809, 0.435, 0.324, 0.402, and 0.289, respectively). **Interpretation and Conclusions:** While a majority of post-COVID patients with diabetic-range hyperglycemia returned to a normoglycemic state after the acute illness had settled down, one in ten developed new-onset diabetes, and an additional one in seven had impaired glucose tolerance. Thus, regular glucose screening is crucial for such patients and lifestyle modifications should be encouraged to reduce the risk of diabetes. Loss to follow-up and reliance on a single set of blood sugar readings for classification were some of the limitations of this study.

Keywords: COVID-19, diabetes mellitus, hyperglycemia, post-acute COVID-19 syndrome, pre-diabetes

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a profound impact on global healthcare infrastructure and human lives. Its relentless spread has led to millions of cases and hundreds of thousands of deaths, challenging healthcare systems worldwide.[1]

While most COVID-19 cases are self-limited, a considerable number of individuals require hospitalization, and a portion of them experience long-term complications even after recovery. Some risk factors associated with severe infections include

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Received: 27-01-2024 **Revised:** 26-04-2024
Accepted: 27-04-2024 **Published:** 26-07-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_140_24

How to cite this article: Agarwal K, Kirti R, Shyama S, Kumar P, Biswas R, Ojha VS. Long-term outcome of patients with diabetic-range hyperglycemia first detected during admission for COVID-19: A single-center observational study. J Family Med Prim Care 2024;13:3374-80.

advanced age, immunocompromised states, and pre-existing lung or heart conditions.[2,3]

Another such risk factor is diabetes. It has emerged as a significant risk factor for severe COVID-19 outcomes. High fasting blood glucose levels at admission have been shown to independently predict the prognosis of COVID-19 cases.[4,5] The relationship between diabetes and SARS-CoV-2 infection is of particular interest, with known diabetes patients requiring more intensive care support.[6]

Additionally, there is ongoing debate about the effect of COVID-19 on the pancreas. Some studies suggest that the virus may directly impact pancreatic beta cells due to the presence of angiotensin-converting enzyme 2 (ACE2) receptors in key metabolic organs and tissues, including pancreatic beta cells.[7,8]

Other studies suggest that COVID-19 may lead to an increased risk of insulin resistance in patients without pre-existing diabetes.[9,10] However, the evidence is inconclusive. It has also been postulated that inflammation induced by the SARS-CoV-2 virus can increase insulin resistance through mechanisms such as lung infiltration by inflammatory cells, leading to acute lung injury, acute respiratory distress syndrome, and potential multi-organ failure in severe COVID-19 cases.[11] This impacts insulin-responsive organs, such as skeletal muscles and the liver, responsible for glucose uptake, consequently contributing to insulin resistance.[12]

Furthermore, steroids, which are commonly used as the principal treatment for moderate and severe cases of COVID-19, significantly elevate blood glucose levels. High-dose steroid treatment in hospitalized patients has been associated with a high incidence of hyperglycemia, leading to insulin resistance and subsequent development of diabetes.[13,14] The impact of dexamethasone on blood sugar levels has been studied, revealing maximal sugar level elevation at 24 h after oral administration.[15] Furthermore, insulin resistance and hyperglycemia are common in patients under stress, especially those with sepsis.[16]

Diabetic-range hyperglycemia has been reported for the first time in many patients during their hospitalization with COVID-19.[17] It is not clear what proportion of these patients have transient hyperglycemia and how many develop diabetes or pre-diabetes in the long run. This study attempts to address this uncertainty. Understanding this relationship will guide clinicians, including primary care physicians, in appropriate treatment and risk estimation for diabetes in the long term.

Thus, this study was undertaken to estimate the proportion of patients who develop new-onset diabetes among those who were first found to have diabetic-range hyperglycemia during hospital stays for COVID-19.

Material and Methods

Study design: This was a descriptive observational study conducted at a hospital in the eastern part of India.

Ethical considerations: The study was conducted after obtaining approval from the Institute Ethics Committee (IEC), in accordance with the principles of the Declaration of Helsinki. Verbal consent was obtained from all participants.

Study participants: Patients admitted with a diagnosis of COVID-19 from July 1 to October 31, 2020, who were found to have blood glucose levels in the diabetic range but were not previously known to have diabetes mellitus, were included in the study.

Inclusion criteria:

1. Age >18 years
2. Admitted to the COVID-19 ward with a positive rapid antigen test (RAT) or real-time polymerase chain reaction (RT-PCR) results for SARS-CoV-2 during the period from July 1, 2020 to October 31, 2020
3. Not a known case of diabetes mellitus
4. Fasting blood sugar (FBS) >/=126 mg/dL, post-prandial blood sugar (PPBS) >/=200 mg/dL, or random blood sugar (RBS) >/=200 mg/dL at presentation or during the hospital stay

Exclusion criteria:

1. Death during the hospital stay
2. HbA1c >=6.5% at or during the admission (classified as previously undiagnosed diabetes mellitus)
3. Refusal to participate

Sampling technique: The complete enumeration technique was adopted. All COVID-19 patients admitted during the study period who were eligible according to the inclusion and exclusion criteria listed earlier were included in the study to avoid selection bias.

Study protocol: A list of all COVID-19 patients admitted during the study period was obtained from the hospital information system. Their case-notes were obtained from the medical records department and screened to identify eligible patients. The latter's socio-demographic details, clinical details (including the need for an intensive care unit (ICU) and the prescription of steroids), investigation results, and other details of treatment were recorded.

Their contact details were retrieved from their admission files, and they were contacted via telephone. The purpose of the call was explained to them, and their verbal consent was sought before proceeding further. Once verbal consent had been obtained, they were asked if they had blood sugar levels checked at least 2 weeks after their discharge or the last dose of steroids, whichever was later. If the tests had been done, the reports were

noted down. Those patients who did not have their blood glucose levels checked after discharge were requested to get their FBS and PPBS tested, and the reports were noted down. Based on their blood sugar levels, the patients were classified into normal, pre-diabetes, and diabetes [Table 1]. Patients with values in the diabetic range were asked about their ongoing treatment and requested to undergo an HbA1c test to assess their glycemic control. Patients with values in the pre-diabetic-range but with reports older than 6 months from the day of the call were asked to undergo a repeat FBS and PPBS. If any patient refused to undergo the requested tests, that information was documented.

Patients with blood sugar levels above the normal range were offered an appointment at the general medicine outpatient department (OPD) of the hospital for further evaluation and management.

Definition of treatment control status

Treatment control status was defined based on HbA1c levels. For patients aged 60 years and older or those with advanced complications or comorbid conditions such as chronic kidney disease, chronic liver disease, cardiovascular disease, etc., a target HbA1c level of <8% was taken as good glycemic control. For all other patients, the target HbA1c level was set at <7%.

Statistical Analysis: The data was entered into Microsoft Excel 2016 (Microsoft Corporation, Inc., Redmond, Washington, USA) and analyzed using the Jamovi software version 2.2.4 (The jamovi project, Sydney, Australia). A descriptive analysis was performed. Continuous variables with a normal distribution were expressed as mean and standard deviation (SD), while continuous variables with a non-normal distribution were expressed as median and interquartile range (IQR). Categorical variables were expressed as proportions. To test the association of different variables with new-onset diabetes, Fisher's exact test was applied, as multiple cells contained values less than 5, necessitating the use of Fisher's exact test over other statistical methods. A *p*-value less than 0.05 was considered significant.

Results

A total of 86 patients were finally included in the study. The chronological flow of the study, with the number of participants at each step, is given in Figure 1.

The demographic and clinical details of the participants are shown in Table 2.

Table 1: Classification of blood sugar levels

Classification	Definition
Normal	FBS* <100 mg/dL and PPBS† <140 mg/dL
Pre-diabetic-range hyperglycemia	FBS 100–125 mg/dL or PPBS or RBS‡ 140–199 mg/dL
Diabetes	FBS >/= 126 mg/dL or PPBS or RBS >/= 200 mg/dL

Footnote: FBS*—Fasting blood sugar, PPBS†—Post-prandial blood sugar, RBS‡—Random blood sugar

The proportion of patients with diabetes, pre-diabetes, and normoglycemia is shown in Table 3. It was further observed that out of the ten patients who had developed new-onset diabetes, eight (80%) were on treatment and five (50%) had their sugar levels under control.

Fisher's exact test was performed to explore any potential associations between new-onset diabetes or pre-diabetes and the various variables, viz., age, gender, comorbidities, ICU stay, and steroid administration. The results are shown in Table 4. No statistically significant associations were found.

Discussion

This study demonstrates that the majority of patients with diabetic-range hyperglycemia initially detected during hospitalization for COVID-19 returned to normal blood glucose levels during follow-up. However, 11.6% of the people did develop new-onset diabetes mellitus, and 15.1% of the patients were in a pre-diabetic state.

The relationship between COVID-19 and long-term diabetes has evoked much interest in recent times. A large study from the United States,[18] examined the post-acute phase of COVID-19 in a cohort of 181,280 participants and two control groups: contemporary (n = 4,118,441) and historical (n = 4,286,911). By the end of a year, 4.08% of the participants who had COVID-19 had developed diabetes. In the same period, 3.10% of the contemporary controls and 3.17% of the historical controls developed diabetes. There was an elevated risk of incident diabetes (a hazard ratio of 1.4 and an excess burden of 13.46 per 1000 people at 12 months) and antihyperglycemic use in patients with a history of COVID-19. A positive correlation was seen with the severity of COVID-19.

A systematic review and meta-analysis of nine cohort studies evaluating new-onset diabetes after COVID-19 infection with data from nearly 40 million people from the United States, England, and Germany found the overall occurrence of diabetes following COVID-19 to be 15.53 (95% CI: 7.91–25.64) per 1000 person-years with a higher relative risk of 1.62 compared to non-COVID-19 patients.[19] Another systematic review and meta-analysis also reported a higher incidence of new-onset diabetes and hyperglycemia following the COVID-19 infection.[20] The incidence was higher among males. It was also influenced by factors like age, ethnicity, timing of diagnosis, and the type of study.

Thus, we see a large variation in the reported incidence of diabetes mellitus after COVID-19. There is a paucity of data from South Asia. Unlike the earlier studies, which aimed to estimate the overall incidence of diabetes after COVID-19, the current study has estimated the proportion of patients with diabetes-range hyperglycemia during COVID-19 who remained hyperglycemic during the follow-up period. The results should be interpreted with caution, given the relatively small sample size. Moreover,

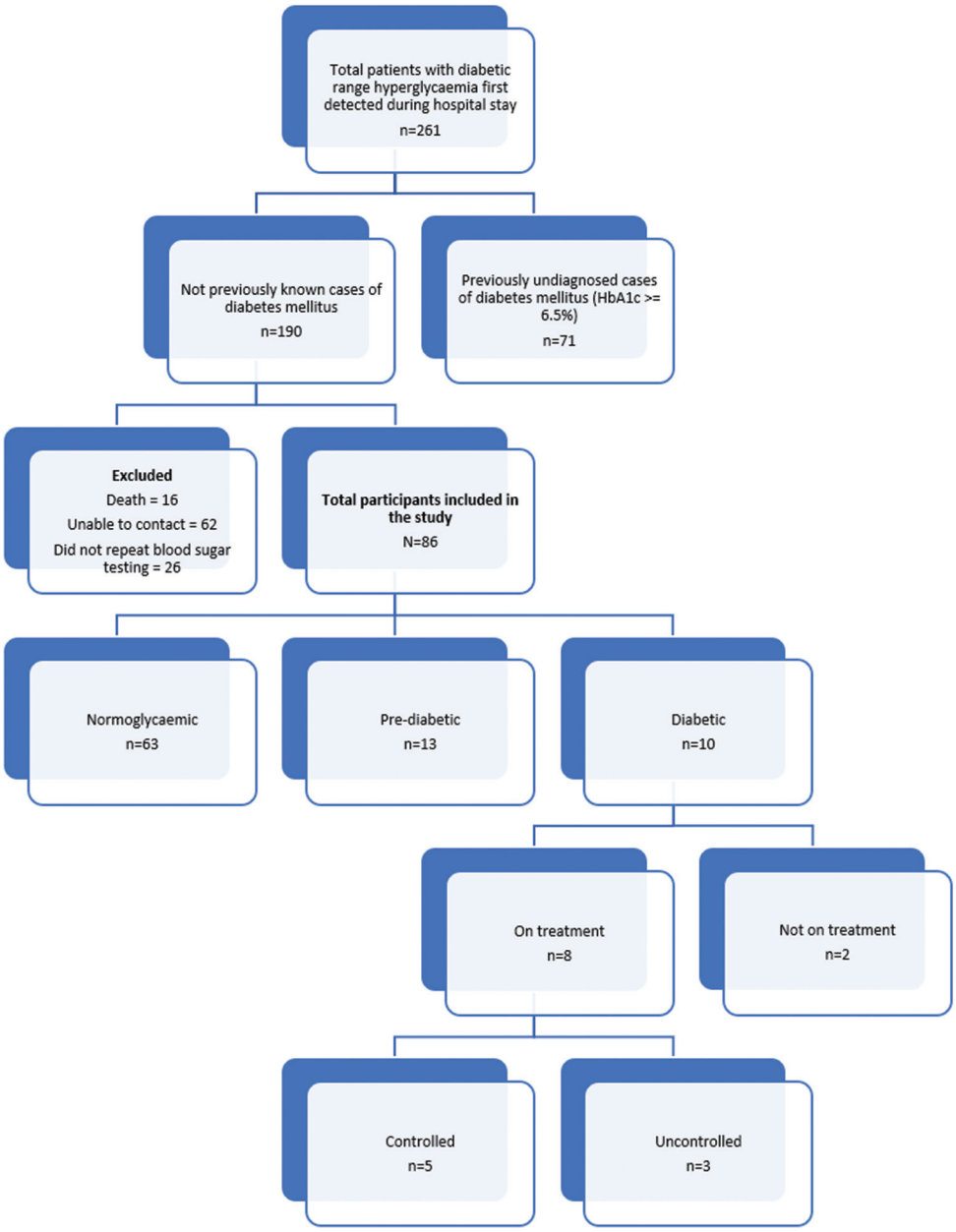

Figure 1: Chronological flow of the study

only hospitalized patients were included in the study, thereby limiting the generalizability of its results.

Another similar study has reported that out of 253 patients who developed new-onset hyperglycemia during their hospital admission for COVID-19, 35% had ongoing hyperglycemia for the following 6 months, and nearly 2% were diagnosed with overt diabetes.[9]

While COVID-19 transiently raises blood sugar levels due to multiple mechanisms, the exact role of the virus in causing long-term diabetes remains unclear. It has been suggested that the SARS-CoV-2 receptor ACE2 and some other entry factors like TMPRSS2, NRP1, and TRFC are present in β cells, with NRP1 showing particularly high expression.[21] Furthermore, SARS-CoV-2 was found to infect human pancreatic β cells in patients who died from COVID-19. It was also reported to selectively infect human islet β cells in laboratory experiments. The study concluded that COVID-19 leads to reduced levels of pancreatic insulin and its secretion, as well as the induction of β cell apoptosis. Notably, these adverse effects were reversed when NRP1 inhibition was done. Thus, it is possible that differential expression of these receptors and entry factors in individuals from diverse ethnicities and geographical regions could lead to variable vulnerability and incidence of diabetes among different populations, further necessitating the need for such studies in different parts of the world.

Stress hyperglycemia is another factor that could potentially contribute to increased blood sugar levels during the COVID-19

infection. The release of cortisol, epinephrine, and glucagon as part of the stress response is known to cause hyperglycemia.[22] This temporary hyperglycemia might cause glucose toxicity in β-cells, further leading to a decline in insulin secretory function both in the short- and long-term, eventually leading to the development of diabetes.[23]

Steroid treatment is widely recognized for its ability to induce hyperglycemia by increasing peripheral insulin resistance and, thus, is another potential mechanism postulated for hyperglycemia during COVID-19 and subsequent development of diabetes.[24] The current study did not find any significant association between the use of steroids and the development of new-onset diabetes. However, as there were very few patients who did not receive steroids, the study was underpowered to detect any difference.

Severe cases of COVID-19 infection, especially those that require mechanical ventilation, are frequently linked to a cytokine storm, characterized by an excessive and uncontrolled release of pro-inflammatory markers like interleukin (IL)-6, IL-1, IL-17, and tumor necrosis factor-alpha.[25] Hence, it is probable that the cytokine storm impacts various organs, including the pancreas, ultimately contributing to the development of diabetes.[24] However, the current study did not detect any significant associations between new-onset diabetes and ICU stays.

This study holds significant implications for clinical practice, particularly in the context of post-COVID-19 care and screening guidelines. It reveals that while many patients with hyperglycemia during COVID-19 hospitalization returned to normal blood sugar levels, a substantial proportion developed new-onset diabetes or were in a pre-diabetic state during follow-up. These findings emphasize the critical importance of ongoing monitoring and intervention for individuals who experience hyperglycemia during their COVID-19 illness. For family practitioners and healthcare providers, this suggests the need for tailored follow-up protocols, including regular blood sugar monitoring and lifestyle interventions, to mitigate the risk of long-term diabetes complications among COVID-19 survivors. By incorporating these strategies into clinical practice and screening guidelines, healthcare professionals can better identify and manage post-COVID-19 metabolic issues, ultimately improving patient outcomes and reducing the burden of diabetes-related complications in this population.

There are certain limitations to this study. Firstly, blood sugars were not routinely measured for all COVID-19-infected

Table 2: Demographic and clinical details of the study participants (N=86)

Variable	Categories	Count (n)	Percentage (%)
Age (years)	Less than 40	12	14.0%
	40 to 60	44	51.2%
	60 and above	30	34.9%
Gender	Male	75	87.2%
	Female	11	12.8%
Comorbidities	Hypertension	33	38.4%
	Hypothyroidism	8	9.3%
	Coronary artery disease	7	8.1%
	Stroke	1	1.2%
ICU stay	Required	25	29.1%
	Not required	61	70.9%
Steroids received during hospital stay	Yes	82	95.3%
	No	4	4.7%
Steroids received at discharge	Yes	79	91.9%
	No	7	8.1%
Duration of hospitalization in days [mean (SD)]	11 (5.31)		

Table 3: Proportion of new-onset diabetes and pre-diabetes among the participants (N=86)

Final Classification	Counts (n)	Proportion (%)	95% Confidence interval of Proportion	
			Lower limit	Upper limit
Diabetes	10	11.6%	6.4%	20.1%
Pre-diabetes	13	15.1%	9.0%	24.2%
Normoglycemia	63	73.3%	63.1%	81.5%

Table 4: Associations between new-onset diabetes with different variables (N=86)

Variable	Categories	Classification			*p*
		Diabetic n (%)	Pre-diabetic n (%)	Non-diabetic n (%)	
Age (years)	Less than 40	1 (1.16%)	3 (3.49%)	8 (9.30%)	0.809
	40–60	5 (5.82%)	7 (8.14%)	32 (37.20%)	
	60 and above	4 (4.65%)	3 (3.49%)	23 (26.75%)	
Gender	Male	9 (10.47%)	10 (11.62%)	56 (65.12%)	0.435
	Female	1 (1.16%)	3 (3.49%)	7 (8.14%)	
Comorbidities	Yes	5 (5.82%)	4 (4.65%)	34 (39.53%)	0.324
	No	5 (5.82%)	9 (10.46%)	29 (33.72%)	
ICU Stay	Yes	1 (1.16%)	4 (4.65%)	20 (23.25%)	0.402
	No	9 (10.47%)	9 (10.47%)	43 (50%)	
Steroids received at or during admission	Yes	9 (10.46%)	12 (13.95&)	61 (70.93%)	0.289
	No	1 (1.16%)	1 (1.16%)	2 (2.32%)	

patients admitted to the hospital during the study period. About a third of the eligible patients (n = 62) could not be contacted due to incorrect or changed contact numbers. Another 26 patients did not get their blood sugar levels rechecked even after being reminded, and hence could not be included in the analysis. The earlier-mentioned factors led to a relatively smaller sample size for the study. As HbA1c levels were not checked in all patients, it is possible that some of the included patients had pre-existing diabetes or pre-diabetes. Finally, the classification into diabetes, pre-diabetes, and normoglycemia was based on a single set of blood sugar readings in the majority of the patients rather than repeated blood tests over a defined follow-up period.

Conclusion

The study found that the vast majority of patients who were first noted to have diabetes-range hyperglycemia during hospitalization for COVID-19 subsequently returned to a normoglycemic state. However, one in ten such patients was noted to have developed overt diabetes on follow-up. Additionally, one in seven such patients had blood sugar levels in the pre-diabetes range. This highlights the need for periodic screening and lifestyle advice in patients who recover from COVID-19, particularly if they had hyperglycemia during the course of their infection. Larger studies are needed for a better estimation of the proportion of patients with diabetic-range hyperglycemia during the COVID-19 infection whose blood sugars remain in the diabetic range during follow-up.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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