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A Study on Newly Diagnosed Hyperglycemia in Hospitalized COVID-19 Patients & its Long Term Impact on Health

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Abstract: ***Background**: Chronic co-morbidities, including diabetes, are highly prevalent in people with corona virus disease 2019 (COVID-19) and are associated with an increased risk of severe COVID-19 and mortality. The phenomenon of new-onset diabetes following admission to the hospital has been observed previously with other viral infections and acute illnesses. Whether new-onset diabetes is likely to remain permanent is not known, as the long-term follow-up of these patients is limited. Our study objectives were (1) to study relationship between new onset diabetes mellitus/hyperglycemia and COVID-19 infections & (2) to study effects of new onset diabetes mellitus/hyperglycemia on prognosis of COVID-19 infection. **Methodology**: It was an observational study in which 100 hospitalized COVID-19 positive cases of newly diagnosed hyperglycemia were selected from civil hospital, Rajkot. Case records & lab records of pt were used for getting information mentioned in questionnaire. Results: Most common age group affected in our study was 41-60 years (44%).70% patients were male. Out of all post-discharged cases, 15 pt expired during 6 months follow up period. Patients whose 'on admission RBS' was more than 500 mg/dl had 100 % mortality rate while it was ~ 43% if 'on admission' RBS was between 400 to 500 mg/dl. At the end of 6 months, 76 out of 85 survived patients had persistent HbA1c value > 6.4 (i. e. developed diabetes). **Conclusion**: as the 'on admission RBS level' rises from 200 mg/dl to >500 mg/dl, mortality rate of patient also rises.90% patients who were non-diabetic at admission had developed diabetes mellitus at the end of 6 months post-discharge period.*

Keywords: newly diagnosed hyperglycemia, hospitalized COVID-19 patients, long term prognosis

1. Introduction

Coronavirus disease 2019 (COVID-19), the highly contagious viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a catastrophic effect on the world's demographics resulting in more than 6 million deaths worldwide as of March 2022, emerging as the most consequential global health crisis since the era of the influenza pandemic of 1918. After the first cases of this predominantly respiratory viral illness were first reported in Wuhan, Hubei Province, China, in late December 2019, SARS-CoV-2 rapidly disseminated across the world in a short span of time, compelling the World Health Organization (WHO) to declare it as a global pandemic on March 11, 2020. Since being declared a global pandemic, COVID-19 has ravaged many countries worldwide and has overwhelmed many healthcare systems [1]. Chronic co-morbidities, including diabetes, are highly prevalent in people with corona virus disease 2019 (COVID-19) and are associated with an increased risk of severe COVID-19 and mortality. Mild glucose elevations are also common in COVID-19 patients and associated with worse outcomes even in people without diabetes. The phenomenon of new-onset diabetes following admission to the hospital has been observed previously with other viral infections and acute illnesses. The precise mechanisms for new-onset diabetes in people with COVID-19 are not known, but it is likely that a number of complex interrelated processes are involved, including previously undiagnosed diabetes, stress hyperglycemia, steroid-induced hyperglycemia, and direct or indirect effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the β-cell. Whether new-onset diabetes is likely to remain permanent is not known, as the long-term follow-up of these patients is limited [2-3]. So we conducted this study to know about HbA1c level at long term follow up (3 month and 6 month post-discharge) and to assess whether having different 'on admission RBS level' has any effect on prognosis of pt or not.

Objectives

- To study relationship between new onset diabetes mellitus/hyperglycemia and COVID-19 infection.
- To study effects of new onset diabetes mellitus/hyperglycemia on prognosis of COVID-19 infection

2. Materials and Methodology

Study type: Observational study

Study place: P. D. U Medical College and civil hospital Rajkot

Study period: 1st March 2020 to 30th September 2021 [19 months]

Sampling method: Purposive Sampling

Sample size: 100 cases of newly diagnosed hyperglycemia in COVID-19 positive patients

A pre-tested semi-structured questionnaire was prepared having questions on important demographic details, presenting complaints, past history, personal history, family history, investigations undertaken, treatment received and outcome of patient. After passing through the filters of inclusion and exclusion criteria, hospitalized patients were selected and details mentioned in questionnaire were recorded from case record during their hospitalization.

Inclusion criteria: all COVID-19 infected non-diabetic hospitalized patients aged >18 yrs, having newly diagnosed hyperglycemia or any of its complications and willing to give informed verbal consent were included in the study

Exclusion criteria: patients not fulfilling inclusion criteria were excluded from study

The permission to do the study was granted by institutional ethical committee.

Lab investigations included complete blood count, renal function test, HbA1c, FBS, PP2BS.

After discharge from hospital, we took follow-up of patients at the end of 3rd and 6th months of admission. On both contact points, we confirmed about post-discharge survival/death of patients and Hb1c levels of that day were recorded in survived patients.

Data Entry was done using MS Excel version 7.0 and analysed using SPSS version 20.0. Frequency, percentage, mean, standard deviation and appropriate statistical tests for significance of association were applied according to the type of data.

Definitions/terminology used in study:
American Diabetes Association (ADA) defines new-onset hyperglycemia without diabetes when fasting plasma glucose (FPG) is between 5.6 and 6.9 mmol/L (100–125 mg/dL) and/or HbA1c is between 5.7 and 6.4%, in absence of dysglycemia in past [4-6].

Since a stress response to an acute viral infection such as COVID-19 can unlikely impact the HbA1c but may increase the plasma glucose, thus a single FPG value of ≥ 7.0 mmol/L (≥126 mg/dL) in absence of HbA1c ≥ 6.5% has been labeled by researchers as new-onset hyperglycaemia without diabetes.

Similarly, new-onset diabetes would be defined in presence of two abnormal samples either FPG is ≥ 7.0 mmol/L (≥126 mg/dL) or HbA1c ≥ 6.5% or a random glucose level ≥ 11.1 mmol/L (≥200 mg/dL) with symptoms of hyperglycemia, in absence of any history of diabetes in past [7].

3. Results

Table 1: Demographic Profile of patients

Particulars	Sub-Group	No. (= %) of patients (n=100)
Age (Years)	12-40 yrs	11
	41-60 yrs	44
	61-80 yrs	34
	81-100 yrs	11
Gender	Male	71
	Female	29
Outcome of patient	Survived	85
	Non-survived	15

Max participants (44%) belonged to 41-60 years. About 70% participants were male. Out of 100 post-discharged cases of COVID-19 infection, 15 expired while 85 survived till 6 months of follow up.

Table 2: Relation between RBS on admission and outcome of patient

RBS on admission	Recovered No (%)	Expired No (%)	Total No (%)	P value of Fischer Exact Test
150-200	17 (89.4%)	02 (10.6%)	19 (100%)	0.00282
200-300	37 (94.8%)	02 (5.2%)	39 (100%)	
300-400	23 (85.1%)	04 (14.9%)	27 (100%)	
400-500	08 (57.1%)	06 (42.9%)	14 (100%)	
>500	00 (0%)	01 (100%)	01 (100%)	
TOTAL	85 (85%)	15 (15%)	100 (100%)	

In this study, we divided patients in 5 groups based on their RBS levels on admission. We can see from the table that there is statistically significant difference between different 'on admission RBS' groups and mortality of patient. Patients who were having on admission RBS more than 500 mg/dl had 100 % mortality rate. Patients with on admission RBS between 400 to 500 mg/dl has mortality rate of ~ 43%. Patients with on admission RBS between 200 to 300 mg/dl had mortality rate of 15%. We can say from the table that as the on admission RBS level rises from 200 mg/dl to >500 mg/dl, mortality rate of patient also rises.

Table 3: Relation of HbA1c levels at different contact points (on admission, 3 months, 6 months) in survived post discharged patients

HbA1c	On Admission	3 Months	6 Months
<6.5	00	04	09
6.5-7	12	09	02
7.1-8	39	29	29
8.1-9	16	29	35
9.1-10	13	11	09
>10	05	03	01
TOTAL	85	85	85

At the end of 3 months, 81 out of 85 patients had HbA1c value of > 6.4 which means they have persistent hyperglycaemia while 4 patients had HbA1c value of < 6.4.

At the end of 6 months, 76 out of 85 patients had HbA1c value > 6.4 that means around ~90 % patients had persistent hyperglycemia fulfilling the definition of new onset diabetes mellitus at the end of 6 months after discharge. So we can say that 90% patients had diabetes mellitus at the end of 6 months post-discharge.

So we can say that 10% patients were having steroids/stress induced hyperglycemia during hospital stay which didn't persist after discharge.

4. Discussion

SARS-CoV2 has been shown to infect and replicate in cells of the human endocrine and exocrine pancreas. Entry of SARS-CoV2 into the beta cells of the pancreas, with subsequent cell destruction, has been postulated to underlie the development of new-onset, insulin-requiring diabetes/hyperglycemia in some patients with COVID19. As with any other acute infection, severe COVID19 is associated with non-specific activation of the immune system, with outpouring of counter-regulatory hormones and pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) alpha, both of which are known to induce insulin resistance and hyperglycemia [8]. Sudden reduction in insulin sensitivity can precipitate diabetes in individuals with borderline beta-cell function and may even manifest as hyperglycemic crises in those with previously undiagnosed (and untreated) diabetes. The COVID-19 patient experienced high stress. Hyperglycemia induced by mild-to-moderate stress is protective since it provides a source of energy for the brain and the immune system in stress conditions. Nevertheless, many of the stress hormone responses result in persistent hyperglycemia and Insulin Resistance, which can be strongly deleterious in the long run. Such mechanism showed its effect in patients of our study too and as a result it happened that at the end of 6 months, 76 out of 85 patients had HbA1c value > 6.4 that means around ~90 % patients had persistent hyperglycemia fulfilling the definition of new onset diabetes mellitus. So we can say that 90% patients had developed diabetes mellitus whose admission time hyperglycemia (HbA1c>6.4) persisted at 6 month follow up period.

In our study, about 70% participants were male while that proportion of the same was 59.3%, 60%, 51% in studies conducted by Gian Paolo Fadini et al [9], Bharat kumar [10] et al and Saygili ES et al [11] respectively. Out of 100 post-discharged cases of covid-19 infection, 15 expired while 85 survived till 6 months of follow up in our study while 90 days mortality in post-discharged patients was 10.2% in study conducted by Saygili ES et al [11].

In our study we observed that Patients who were having on admission RBS more than 500 mg/dl had 100 % mortality rate. Patients with on admission RBS between 400 to 500 mg/dl has mortality rate of ~ 43%. Patients with on admission RBS between 200 to 300 mg/dl had mortality rate of 15%. We can say from the table that as the on admission RBS level rises from 200 mg/dl to >500 mg/dl, mortality rate of patient also rises.

In the study conducted by Saygili ES et al [11], Patients were divided into groups according to the ABG level (Admission time Blood glucose level). Groups 1, 2, and 3 have ABG level of <100 mg/dL, 100-139 mg/dL, and 140-199 mg/dL, respectively. From groups 1 to 3, in-hospital mortality, 30-day mortality, and 90-day mortality rates increased as blood sugar increased.

A study conducted by Bharat kumar et al [10] showed that new onset of hyperglycemia acted as bad predictor of mortality between survived and non-survived group (i. e. patient's outcome). (8.7% Vs 60%, p<0.0001). Mortality from COVID-19 showed increasing trend with rising random plasma glucose levels at admission (0.6, 2.0, 13.9 and 28.0% in patients with random plasma glucose of <100, 100–200, 200–300 and >300 mg/dL, respectively; P = <0.0001).

A study conducted by Gian Paolo Fadini et al [9] showed that for each 2 mmol/l higher FPG, there was a significant 19% lower probability of recovery (HR 0.82 95% C. I.0.74–0.91; p < 0.0010). So our study also shows similar finding of rising mortality in line with rising admission time blood glucose as the existing studies found.

5. Conclusion

At the end of 6 months, ~90% post-discharged COVID-19 patients had persistent hyperglycemia with hbA1c values more than 6.5 which suggests 90% of patients had diabetes mellitus at the end of 6 months. As the 'on admission RBS level' rises from 200 mg/dl to >500 mg/dl, mortality rate of patient also rises consistently with the highest mortality rate (100%) when the on admission RBS is >500mg/dl. Patients with higher blood sugar levels (>=300 mg/dl) carry poor prognosis (non-survival during 6 months of follow up) in comparison to those 'on admission RBS level <300 mg/dl.

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