Hyperglycemia as a Complication of COVID 19: An Observational Study

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Abstract

Background: Hyperglycemia has got a bidirectional importance in COVID 19, on one end it causes aberrant glycation of ACE receptors in lungs causing more severe disease and on other end it may occur as a result of complication of disease itself.

Objective: To determine whether hyperglycemia is a complication of COVID-19.

Methodology: A cross sectional observational study was conducted on 126 admitted, moderate to severe COVID-19 patients, to observe new onset hyperglycemia in relation to their previous glycemic control (glycated hemoglobin levels HbA1c). Blood sugar random (BSR) noted at time of admission was taken as dependent variable and HbA1c, body mass index and severity of disease as independent variables to find out association. Patients who were known diabetic and already taking steroids were excluded from study.

Results: A total of 126 patients (66 male and 60 female) included in the study with a mean age 56.9 yrs. ± 11.8. Based on admission HbA1c, 71(56.4%) patients were non-diabetic, 35(27.7%) pre-diabetic, and 20(15·9%) were diabetic. Initial random blood sugar revealed overall 31(24.6%) patients had normoglycemia, while 95(75.4%) had hyperglycemia, more precisely 67(53.2%) had moderate and 28 (22.2%) had severe hyperglycemia. Hyperglycemia was observed among 9 out of 12 (75%) patients from 20-39 years age group, 51 out of 61 (83%) patients from 40-59 years age group and 35 out of 53 (66%) from 60-75 years age group. Eighty percent male and 76% female had hyperglycemia. Nineteen (15%) were of normal weight, 79 (62.8%) overweight and 28 (22·2%) were obese. The moderate and severe hyperglycemia for 95(75%) patients showed that 49(51·6%) had non-diabetic HbA1c, 27(28·4%) had prediabetes HbA1c and 19 (20%) had diabetic range HbA1c. Further linear association was determined between BSR and HbA1c, p<0001. Among 31 normoglycemic patients it was found that 13(41.9%) patient were of normal weight, 17(54.8%) patients were overweight and one (3.3%) patients was obese. Moreover, Body Mass Index (BMI) and severity of disease were found to have significant association with new onset hyperglycemia with P<0·001 and P=0·01 respectively.

Conclusion: There is an association between new-onset hyperglycemia and moderate to severe COVID-19 disease. Follow-up studies are required to prove the diabetogenic effect of COVID 19.

Keywords: COVID 19; Complication, Admission Hyperglycemia; Diabetes.

Introduction

COVID 19 has been hitting the humanity since its first case was identified in Wuhan city of China in December 2019. It has affected the people around the globe including Pakistan. Till 10th July 2021 more than 186 million people had been affected with a mortality rate of approximately 2.16%. More than 4 million people had died because of this merciless virus and this unseen enemy has become a serious life threat to whole world. It is coming in waves with different variants having different virulence. Though more than 1.9 billion population has been vaccinated till date, a lot of concerns with mortality associated with new variant i.e., delta virus, even in those patients who had been vaccinated are still there[1].

Type 2 diabetes mellitus (T2DM) has been identified as a great risk factor for severity of disease and increased mortality. Other aspects of disease in relation to hyperglycemia are yet to be studied, like new onset hyperglycemia in moderate to severe disease that may arise concerns about new onset diabetes or COVID induced diabetes in some patients.[2] Finding of new onset hyperglycemia in previously non-diabetic patients and resistant hyperglycemia requiring high dose of insulin for glycemic control, points towards its diabetogenic effect beyond the stress response related to severe disease. Almost 70% to 80% of infected patients have mild symptoms or no symptoms, 20% patients enter into pulmonary

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phase and develop pneumonia, out of which 5% patients require intensive care and may die of complications.[3] A lot of risk factors have been identified for poor prognosis of disease, among those diabetes mellitus has been identified as the most important risk factor.[4]

Among admitted patients, hyperglycemia was a commonly observed finding in many patients. Even those who were not previously diagnosed case of diabetes or prediabetes also developed hyperglycemia urging to start oral hypoglycemic agents or insulin for glycemic control regardless of being given intravenous steroids or not. Therefore, there could be three possible scenarios. Firstly, the patient already has diabetes, but it has not been diagnosed yet.[5] Secondly, the patients have prediabetes and acute inflammatory response triggered by SARS Cov 2 and steroids have just pushed these patients into hyperglycemia.[6] Thirdly, patients were non diabetic recognized by their glycated hemoglobin (HbA1c) but they were genetically at risk because of being overweight or having sedentary life styles, hence the disease triggered inflammatory response, beta cell damage in pancreas and increased insulin resistance had led them into hyperglycemia.[6] In Literature, hyperglycemia as a cause of severe disease is well documented but its importance as a complication of disease still requires further investigations. Hence, this study was planned to determine whether hyperglycemia is a complication of moderate to severe COVID pneumonia.

Methodology

A cross-sectional observational study was conducted at Sir Sadiq Abbasi Hospital, Bahawalpur, during the period of 15 April to 15 June 2021. It included PCR positive and High Resolution Computed Tomography (HRCT) suggested COVID 19 patients admitted in High Dependency Unit (HDU). At 95% level of confidence, 5 % margin of error and 9% estimated population proportion, the calculated sample size was 126. After getting an approval from institutional ethical committee, patients of either sex, admitted to High Dependency Unit with moderate to severe disease who gave informed consent, were included by convenience

sampling. Patients who were already diagnosed with diabetes or pre-diabetes or who had received intravenous or oral steroids prior to hospitalization were excluded from the study. All the participants had baseline randome blood sugar and HbA1c at the time of admission. According to age, patients were categorized into 3 groups, 20-39 years, 40-59 years, and 60-75 years. Based on the results of the initial (on admission) blood sugar random (BSR), patients were categorized into three groups: lesser than or equal to 180 mg/dl was considered as normo-glycemia, 180 to 299 mg/dl as moderate hyperglycemia, and >300 mg/dl as severe hyperglycemia. Based on the results of initial HbA1c, patients with 4 to 5.69% were considered non-diabetic, while those with HbA1c values between 5.71 and 6.49% were considered pre-diabetic and >6.5% were considered diabetic.[7]

Those who require oxygen to maintain Oxygen saturation SpO_2 >90% with respiratory rate of more than 20/min and having more than 50% lung involvement on HRCT were considered to have severe disease , while patients having SpO2 >95% at room air with normal respiratory rate and having >50% lung involvement on HRCT as moderate disease.[8] Body mass index (BMI) of 18·5-24·9 kg/m² as normal weight, BMI of 25-29·9 kg/m² as overweight and BMI >30 kg/m² was taken as obesity. SPSS version 20 was used for data analysis, in which age, gender, severity, BMI, HBA1c, BSR and severity were taken as categorical variables. Descriptive analysis was done and frequencies were determined as Mean and Standard Deviation. We applied Chi- square test of significance taking P value < 0·05 as significant. The association was determined by using linear regression analysis.

Results

A total of 126 patients were included in the study. Sixty-six (52.4%) were male, whereas 60 (47.6%) were female. Twelve (9%) patients were between the ages of 20 and 39, sixty one patients (48%) were between the ages of 40 and 59, and 53 (42%) were between the ages of 60 and 75, with mean age of 56.9 years SD ±11·84. There were 57 (45.2%) patients who had no comorbid factors. Among the 69 (54.8%) with comorbid conditions, 25 (19·8%) patients had hypertension (HTN), 14 (11·1%) were obese, 11 (8.7%) had Ischemic heart disease, 9 (7.1%) were old age, 4 (3.2%) had chronic obstructive pulmonary disease, 2 (1.6%) had asthma, and 2 (1.6%) had

chronic kidney disease. Twenty-two (17.5%) patients had moderate disease whereas, 104 (82.5%) patients had severe disease. The real time PCR was positive for 72(57%) patients and 54(42%) were negative but they were diagnosed on the basis of clinical history and HRCT findings. The glycemic level of patients showed that 31 (24.6%) patients had normoglycemia, 67 (53.2%) moderate hyperglycemia and 28 (22.2%) had severe hyperglycemia. Depending upon HbA1c 71 (56.4%) patients were non-diabetic, 35 (27.7%) pre diabetic, and 20 (15·9%) were diabetic with HbA1c >6·5%. Nineteen patients (15%) were of normal weight, 79 (62.8%) were overweight and 28 (22·2%) were obese. The relation between BSR and HbA1c is shown in Table

Table I: Blood sugar levels among groups of patients according to their HbA1c levels.

Blood Sugar Random(mg/dl)	Classification based on HbA1c%			
	Nondiabetic (<5·6%) n = 71	Prediabetic (5·7 - 6·4%) n = 35	Diabetic (>6·5%) n = 20	Total n =126
Normal BSR (<179)	22(31%)	8(22.9%)	1(5%)	31
Moderate Hyperglycemia (180 -299)	45(63.4)	19 (54.2%)	3(15%)	67
Sever hyperglycemia (>300)	4(5.6%)	8(22.9%)	16(80%)	28

Overall, moderate or severe hyperglycemia was found in 95 (75%) patients. As shown in Table 1, among the patients having HbA1c in diabetic range, only 5% have normal glucose level, while 15% had moderate hyperglycemia and 80% had sever hyperglycemia. Among the patients having HbA1c in pre-diabetic range, 22.9% have normal glucose level, while 54.2% had moderate hyperglycemia and 22.9% had sever hyperglycemia. On the other hand, among the patients having HbA1c in non-diabetic range, 31% have normal glucose level, while 63.4% had moderate hyperglycemia and only 5.6% had sever hyperglycemia.
Among 31 normoglycemic patients it was found that 13(41.9%) patient were of normal weight, 17(54.8%) patients were overweight and one (3.3%) patients was obese. Among patients with moderate hyperglycemia 5(7.4%) were of normal weight, 45(67.2%) were overweight, 17(25.4%) were obese. Out of 28 patients having severe hyperglycemia, 1(3.6%) had normal weight,

17(60.7%) were overweight and 10(35.7%) were obese. So, it was found that moderate and severe hyperglycemia was common in overweight patients as compared to normal weight individuals with p value <0.01.
Hyperglycemia was observed among 9 out of 12 (75%) patients from 20-39 years age group, 51 out of 61 (83%) patients from 40-59 years age group and 35 out of 53 (66%) from 60-75 years age group. Fifty three out of 66 (80%) male patients and 43 out of 60 (76%) female patients were found to have hyperglycemia. No significant association was seen between comorbid factors and hyperglycemia. The severity of disease as determined by HRCT chest was significantly associated with BSR (P= 0·01).

Discussion
Current study revealed that three quarter (75%) patients having moderate to severe COVID-19 disease had moderate or severe hyperglycemia on admission. Despite the fact that those with known history of diabetes or prediabetes and those already on steroid before admission were excluded, still there were significant number of patients whom admission HbA1c fall in prediabetic (28%) or diabetic (16%) range. It signifies the lack of awareness of public and poor medical services, unable to diagnose diabetes earlier. Even if only those patients who had normal HbA1c on admission were considered, 63.4% had moderate hyperglycemia and 5.6% had severe hyperglycemia. An overall 69% hyperglycemia sounds quite alarming. A study from Athens, Greece by Ilias L et al. also found higher glucose level on admission in substantial number of COVID -19 patients admitted in ward or ICU.[9]
As shown in Table 1, 63.4% patient in nondiabetic group had moderate hyperglycemia and 5.6% had severe hyperglycemia as compared with those with HbA1c in diabetic range who had moderate hyperglycemia in 15% and severe hyperglycemia in 80%. Furthermore, hyperglycemia was more prevalent among patients who were overweight or obese compared to those of normal weight. Hyperglycemia causes an aberrant glycation of ACE receptors which are binding sites for SARS- COV-2 causing their up regulation and more binding of viruses to receptors leading to severe inflammatory response and increase in severity of disease.[10] Morphological changes also occur in pancreatic beta cells as they also have ACE receptors. Endocrine portion of pancreas becomes permeable to SARS-

COV-2 via binding sites, leading to redox stress and inflammatory response in beta cells leading to destruction and apoptosis of beta cells. This causes partial insulin deficiency and also increased resistance to available insulin.[11,12] There may be another possible mechanism for acute hyperglycemia which was observed in previous coronavirus disease like Middle eastern Respiratory Syndrome MER. MERS Corona virus binds with Dipeptidyl peptidase DPP4 which is an enzyme responsible for modulation of insulin action by degradation of incretin like Glucagon like Peptide 1(GLP 1).[13]

In this study hyperglycemia was common in males, overweight to obese patients, in middle and older age group as compared to young age group. Overweight to obese range BMI is also found to be a risk factor for non-diabetic and prediabetic patients to develop hyperglycemia as found in previous studies.[14] Moreover, hyperglycemia was observed more frequently in severe cases as compared to moderate cases establishing its relation to severity of disease i.e., with increasing degree hyperglycemia more sever disease was observed. In a review article Michalakis and Ilias described the phenomenon for causing hyper glycaemia in COVID 19 patients. Hyperglycemia in turn causes the increased ACE receptors activation leading to Radical Oxygen Species (ROS) activation which causes further inflammatory response by increasing viral replication and worsening the situation.[15]

Literature shows that persistent hyperglycemia is predictor of increased severity of disease, as it can lead to increased inflammatory response causing increased mortality.[12] Moreover, several other factors of disease like stress of acute illness and intravenous steroid therapy were supposed to be the reason for causing short term hyperglycemia in these patients.[16] In present study hyperglycemia was observed in non-diabetic patients who had previously normal glycated hemoglobin levels and even if intravenous steroids were not started in these cases. So, new onset hyperglycemia in COVID patients may be a complication of disease itself.[17]

There are few limitations of this study including small number of patients, only moderate to severe disease included and a single center study. Although prior use of steroid was an exclusion criteria in this study, but considering the prescribing practices and self-medication prevailed during the pandemic, some patient might have received steroids.

To prove this association of hyperglycemia and COVID-19 disease / secondary diabetes, more, larger, multicenter studies are needed. Furthermore, follow up of those patients who develop hyperglycemia required to find out whether it persist or settle after recovery.

Conclusion

Findings of this study revealed an association between new-onset hyperglycemia and moderate to severe COVID-19 disease. Follow-up studies are required to observe that it persist after recovery and prove the diabetogenic effect of COVID 19.

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