Continuous Blood Glucose Monitoring to Determine the Glycemic Variability in Patients Having SARS CoV-2 Infection with ARDS and Its Bearing on the Severity of the Disease

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aims and Objectives: A study to determine the effect of glycemic variability measured by continuous blood glucose monitoring as assessed by standard deviation of each SARS CoV -2 patient's mean glucose level and to correlate with the severity of the disease.
Study Design: Cross-sectional observational study of 13 patients with SARS CoV-2 infection with Acute Respiratory Distress Syndrome (ARDS) with and without diabetes.
Place and Duration of Study: Department of Medicine, Dhiraj Hospital, Smt. Bhikhiben Kanjibhai Shah Medical College and Research Institute; between June 2020 to July 2020.
Results: 13 patients of SARS CoV-2 with ARDS were enrolled in the study. The median age of the enrolled patients was 55±12 years. Out of the 13 patients, 5 patients belonged to mild and severe

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category of ARDS each respectively and 3 patients belonged to the moderate category of ARDS. There was a gradual rise in inflammatory markers such as serum LDH, Ferritin, CRP from mild to severe ARDS and D-dimer level was more than double in severe category as compared to the mild ARDS. Normal glycemic variability in adults is 0-3 SD, and we found that there was a significant co-relation of glycemic variability with severity of the disease evidenced by the mean standard deviation of severe ARDS patients as 27.44 SD; whereas 19.26 SD and 9.7 SD for moderate and mild ARDS patients respectively. Hypoglycemia was documented in 10 patients. The maximum stay in the hospital was that of the patients with high glycemic variability that is 22 ± 2 days

Conclusion: This preliminary study relates glycemic variability with severity of ARDS in patients of severe SARS CoV-2. Frequent episode of hypoglycemia is not uncommon and should be monitored.

1. INTRODUCTION

COVID 19 has become an illness of the household, affecting the entire world, affecting millions of people and one of the most important cause of death in year 2020.More than seventeen million people affected in the world, of which 6.68 lakh people died upto July 2020,mortality rate of 3.93% [1]. India, a thickly populated country had 1.6 million cases of Covid 19 of which death occurred in 2.18% patients upto July 2020 [2]. Presentation of clinical cases in India to start with was very typical like fever, mild upper respiratory tract infection, headache and body ache and reported to have relatively mild course. However, patients aged ≥60 were considered at significant higher risk of mortality [3,4]. influenza-like illness (ILI) and severe acute respiratory infections (SARI) was considered an important key point for screening and diagnosing Covid-19, many atypical clinical features were noted and then was established as an important key symptom of Covid-19 like disturbance in sense of taste and smell, which was part of involvement of nervous system [5,6,7]. Confusion, headache and occurrence of stroke was due to involvement of CNS [8]. GIT symptoms like diarrhoea nausea and vomiting and others are described features of Covid-19 [9].

Diabetes in COVID-19 infected patients have poor prognosis both type 2 and also type 1 which can be e multifactorial [10]. Diabetes as well as sepsis in Covid-19 is considered pro-coagulative state. Covid menifestations include acute metabolic Complications due to beta cell dysfunction leading to diabetic ketoacidosis, admissionhyperglycaemia and also new onset diabetes [10,11,12].

Glycaemic variability, a marker of glucose homoeostasis in the body can be determined by continued glucose monitoring (CGM) which gives short term glycaemic variability, or by serial estimations of HbA1c which gives long term glycemic variability [13]. This short study tries to examine glycemic variability in covid -19 positive patients in our set-up and to establish a correlation between the glycemic variability with the severity of the ARDS in the SARS-CoV2 patients, with or without diabetes.

2. METHODOLOGY

This study is a cross sectional observational study of 13 patients with severe SARS-CoV-2 infection with and without diabetes who were admitted in Covid ICU in Dhiraj Hospital from 25 June 2020 to 4 July 2020 patients. All severe SARS-CoV-2 infected patients were further classified as Mild ARDS, Moderate ARDS and Severe ARDS according to PaO2/FiO2 ratio. Mild ARDS: 200 mmHg < PaO2/FiO2a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O), Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O), Severe ARDS: PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O). "Freestyle Libre Pro Flash Glucose Monitoring System Sensor" was placed with a subcutaneous attachment on the left arm of the patient. Continuous glucose monitoring was done for 5 days for all patients by the attached device. Hypoglycemia Data was analyzed Freestyle Libre Pro Flash Glucose Monitoring System reader, Demographic and clinical variable analyzed included age, gender, previous history of Diabetes, use of Remedesivir, Tocilizumab, Convalescent Plasma therapy included.

All 13 patients were given standard treatment of SARS-CoV-2 along with broad spectrum antibiotics and inj methyl prednisolone 80 mg/day.

Hypoglycemia was defined as any episode of blood glucose level less than 80 mg/dl during hospital stay. Persistent hyperglycemia was consider when blood glucose level more than 180 mg/dl [14] in more than 50% of readings. Mean glucose level (MGL) and standard deviation (SD) of each patients was documented. Normal reference ranges was considered as mean glucose in mg/dl±2 SD for glycemic variability. Normal range of glycemic variability as derived by this method was 0-3.0 in non-diabetic individual for this study [15] Statistical analysis was perform using 'CDC EPIINFO'.

3. RESULTS

During the study, 13 SARS-CoV-2 of Severe category, who were in Covid critical care unit were enrolled. Median age of enrolled patient was 55±12 years, out of which, 76% were male, 2 patients were known cases of diabetes with HbA1C of 6.2-6.7; and both these patients were already on Oral Hypoglycemic Agent – Tablet Metformin 500 mg BD. There diabetes was under control and both belonged to the mild category of ARDS. All the patients enrolled were given standard SARS-CoV-2 treatment as per the protocol along with Injection Methyl Prednisolone 80 mg/day intravenously. The patients enrolled were divided into Mild ARDS, Moderate ARDS and Severe ARDS according to PaO2/FiO2 ratio. Out of which 38.4% were SARS-CoV-2 with mild ARDS, 23.2% had SARS-CoV-2 moderate ARDS and 38.4% SARS-CoV-2 severe ARDS (Table 1). There was a gradual but evident rise in the inflammatory markers namely serum LDH, CRP and Ferritin levels from mild to severe ARDS where as d-dimer level of severe category was more than double as compared to the mild category (Table 2).The standard deviation of each patient's Mean Glucose Level (MGL) was calculated and this value used as deflection for patients glycemic variability (Table 3).

Normal glycemic variability in adults was considered as 0-3.0 SD in non diabetic individual [15]. We found that there was a significant correlation of glycemic variability with severity of disease (p value ~0.003). Mean standard deviation of severe ARDS patient was 27.44 mg/dl, that of moderate ARDS patient was 19.26 mg/dl and for mild ARDS patient, it was 9.7 mg/dl. Hypoglycemia was documented in 10 patients (76.9%) out of which 31 % had severe ARDS, 18% had moderate ARDS and 15% had mild ARDS. Persistent hyperglycemia was documented in 15.38% patents; and all of them belonged to the severe ARDS category.

Table 1. Demographic and clinical characteristics of patients

	Number	Percentage
Age (median)	55 ±12	
Male	10	76.92%
DM II	2	15.38%
Mild ARDS	5	38.46%
Moderate ARDS	3	23.07%
Severe ARDS	5	38.46%
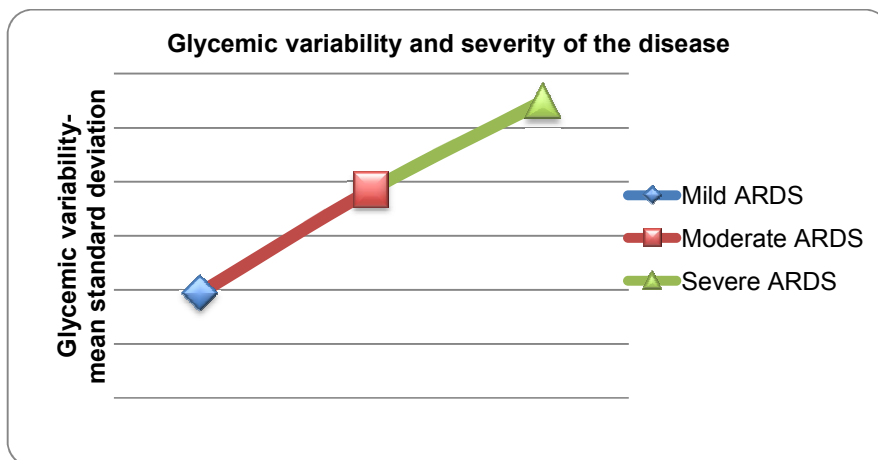
Fig. 1. Glycemic variability and severity of the disease

Table 2. Inflammatory markers

	Mild	Moderate	Severe
LDH (U/L)	660 ± 67	898 ± 31	928 ± 62
CRP (mg/L)	127 ± 59	137 ± 51	142 ± 15
FERRITIN (ng/ml)	502 ± 56	597 ± 166	799 ± 85
D-DIMER (ng/ml)	536 ± 80	1140 ± 171	1350 ± 173

Table 3. Glycemic variability and severity of the disease

Severity of disease	Mean glucose level (MG/DL)	Mean standard deviation from MGL (Glycemic vaiability)
Mild ARDS	90.04	9.7
Moderate ARDS	114.67	19.26
Severe ARDS	172.00	27.44

It was also observed that the hospital stay of severe category patient having high glycemic variability was the maximum (22±2 days) as compared to the mild ARDS patients who had the minimum hospital stay (13±3 days).

4. DISCUSSION

Glycemic variability, concept of glycemic excursions and comparing mean glucose value in comparison to ideal glucose is measured by various formulae. One of the most easy method is of Standard deviation (SD), an index of dispersion of glucose value from average, is commonly used in clinical practice [15,16]. It was also used in this study. It can be used for SMBG using seven point blood glucose monitoring. Coefficient of variation (CV) is another method which corrects for the mean. Mean amplitude of glycemic excursions (MAGE) and Continuous overall net glycemic action (CONGA) specifically used for CGMS [15,16,17]. MAGE <3.9 mmol/L (70.2 mg/dl) and SD <1.4 mmol/L (25.2 mg/dl) are recommended as the normal reference ranges for glycemic variability in Chinese adults [16]. Ideally normal ranges for any method being used to assess glycemic variability is defined as the mean±2 SD [15,18].

In this study we found that the glycemic variability, defined as the standard deviation of the Mean Glucose Level obtained from continuous glucose monitoring in SARS CoV-2 patients during ICU stay had a strong correlation with the severity of the ARDS. The similar results were obtained by James S Krinsley in a study done on critically ill patients in which he found that high glucose variability was firmly associated with ICU and in-hospital mortality [19].

Jeroen et al. also concluded in their study that, glycemic variability plays an a very important role in association with the prognosis of the critically ill patients [20]. Specifically, Ferreira et al. in their study accounted the impact of glycemic variability in diabetic patients with Community Acquired Pneumonia and COPD [14].

Extensive data indicates that in-patient hyperglycemia is also associated with poor clinical outcomes such as mortality, infections, increased hospital stay and other complications. In our study, 15% had persistent hyperglycemia (>180 mg/dL) during hospitalization suggesting a poor glycemic control which may be due to inflammatory cytokines i.e. cytokine storm as a result of SARS Co-V2, stress hormone which inhibit insulin release and promote insulin resistance thereby naturally increasing the blood glucose. In addition, many drugs further promote hyperglycemia including the administration of corticosteroids which was given to all the patients. Atleast one episode of hypoglycemia (<80 mg/dL) was documented in 76.9% which may be due to non-invasive ventilation and loss of appetite as a result of SARS Co-V2. Continuous glucose monitoring allows the evaluation of the patient's response to treatment and compliance with glycemic goals.

All 13 patients had ARDS based on hypoxemia criteria and were divided into mild, moderate and severe ARDS [21] Glycemic variability measured by mean blood sugar with SD was showing higher glycemic variability in relation to severity of ARDS. The reinforcement or strategies to maintain the euglycemic state for SARS Co-V2 patients may lead to better prognosis as glycemic variability can be considered as a treatable risk factor in SARS Co-V2 infection.

This small pilot work of glycemic variability in covid patients with ARDS gives insight about glucose metabolism, hypoglycemia and hyperglycemia in relation to ARDS in covid virus infections. Among important risk factors for covid suspectibility and complications are diabetes and increased BMI which can be linked to poor immunity,stress hyperglycemia,and/or pancreatic damage [22]. As per protocol adopted in our center for ARDS patients all patients received steroids,especially dexametasone and glucose monitoring was essential in all such cases. Dexamethasone is considered as one of the drug to improve survival in COVID-19 [23]. Glycemic effect of dexamethasone starts in about 3 hrs and glycemic peak occurs after 9–10 h which may cause glycemic variability.Monitoring this variability and use of correctional insulin for management can lead to normal glucose homeostasis [24]. Chloroquine and hydroxychloroquine use in covid can lead to decrease in glucose levels [25]. Role of DPP4 inhibitors, which can inhibt realase of IL-6 and TNF-α in ARDS without producing much glycemic variability is a interesting proposition [26]. CGM may thus help to manage both extreme of glucose fluctuation due to Covid-19 virus, due to associated multi-organ dysfunction syndrome, due to associated diabetes and/or drugs used for immunomodulaton.Larger study is recommended to get better insight about glycemic varibity and its relation to in-hospital hyperglycemia, drug related glycemic excursions and the outcome of covid affected patients.

5. CONCLUSION

This preliminary study relates glycemic variability with severity of ARDS in patients of severe SARS CoV-2. Frequent episode of hypoglycemia is not uncommon and should be monitored.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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