Original Article

Outcome of COVID-19 in Type 2 Diabetics : A Cross Sectional Study

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Background : Presences of diabetes mellitus and cardiovascular diseases has been associated with increased risk of COVID-19 disease severity and worsening outcomes, including high mortality. Different therapeutics option for treating COVID-19 can further affect glucose metabolism. To understand a few perspectives of relationship between diabetes and COVID 19, the present study was conducted to explore the outcome of COVID-19 in type 2 diabetics.

Methods: A cross sectional multicentric study was conducted on outdoor and indoor T2DM patients diagnosed with COVID-19 who were assessed for their demographic data, metabolic measures and duration of diabetes. Outcomes were assessed using ACTT version 2 WHO Ordinal scales on day 10 and day 15 of symptoms onset. Association between COVID-19 outcome and various factors like glycemic statuses, BMI, ongoing anti diabetes therapy and concomitant use of statin and anti-platelet drugs were explored.

Results : A total of 248 diagnosed COVID-19 diabetic patients were included for the study. Hospitalization was noted in 82.25% cases, while 20.97% cases needed mechanical ventilation. In 27 deaths were noted. Significant positive association was observed only for BMI (p=0.05) at Day 15, while rest association measures were non-significant. Drug Usage pattern suggested maximum use of metformin, followed by glimiperide and insulin. Other antidiabetic agents prescribed included canagliflozin, voglibose, linagliptin, sitagliptin, teneligliptin and vildagliptin.

Conclusion: Tight glycaemic control and management of cardiovascular risk factors are imperative for COVID-19 patients with T2DM. Co-existence of COVID-19 and T2DM can further worsen the clinical outcomes, hence management approaches must exert caution and should be individualized.

[*J Indian Med Assoc* 2023; **121(7):** 61-4]

Presences of diabetes mellitus and cardiovascular diseases has been associated with increased risk of COVID-19 disease severity and worsening outcomes, including high mortality. Defect in glucose homeostasis, inflammation, immune dysregulation and activation of the Renin–Angiotensin–Aldosterone System (RAAS) were potential contributors which linked COVID-19 and Diabetes Mellitus (DM). Tight glycemic control during the COVID-19 pandemic and prevention of micro and macrovascular complications of diabetes would have been crucial in diabetic patients

> **Editor's Comment :**
> - Tight glycaemic control and management of cardiovascular risk factors are imperative for COVID-19 patients with T2DM.
> - Different therapeutics option for treating COVID-19 can further affect glucose metabolism.
> - Co-existence of COVID-19 and T2DM can worsen the clinical outcomes, hence management approaches must exert caution and should be individualized.

for prevention of severe courses of COVID-19. Postulations suggest that hyperglycemia directly increases SARS-CoV-2 replication in human monocytes, which is further sustained by glycolysis via the production of mitochondrial reactive oxygen species. Activation of hypoxia-inducible factor 1α also plays critical role to support viral proliferation[1]. According to various studies hyperglycemia or a history of Type 1 DM (TIDM) and Type 2 DM (T2DM) were independent predictors of morbidity and mortality in patients with SARS. Diabetic patients represented higher categories of SARS-CoV-2 infection severity compared to non-diabetics. Need for medications and hospitalizations were thus increased in presence of poor glycemic control which also predicted increased mortality. SARS CoV 2 infection caused increase in Reactive Oxygen Species (ROS) production. Increase in ROS and IL 6 production further cause rise in insulin

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resistance and RAAS activation leading to hyperglycemia and vascular endothelial damage[2].

As a part of management, insulin and dipeptidyl peptidase 4 (DPP4) inhibitors were safer alternatives in diabetic patients suffering from COVID-19. In patients at high risk of severe disease it is better to de-prescribe metformin and sodium– glucose cotransporter 2 inhibitors[3]. Furthermore, obesity - a common comorbid condition associated with T2DM – has also been linked. Studies suggested that obese population having phenotype of chronic inflammation have high risk of developing COVID 19 related inflammations[4]. Different therapeutics option under investigation to treat COVID-19 including corticosteroid affect glucose metabolism. This requires careful approach particularly in patients with DM and needs to give importance on frequent structured blood glucose monitoring and personalized adjustment of anti-diabetes medications. To understand a few perspectives of relationship between diabetes and COVID 19, the present study was conducted to explore the outcome of COVID-19 in T2DM patients.

MATERIALS AND METHODS

A cross sectional multicentric study was conducted in few tertiary care hospitals of Kolkata and Mumbai. Permission to conduct the study was obtained from the institutional ethics committee prior commencement. Written informed consent was obtained from participants consenting to be the part of this study. All consenting outdoor and indoor T2DM patients diagnosed with COVID-19 [Real Time Polymerase Chain Reaction (RT PCR) positive patients] were included for the study. Those not willing to participate or not able to comprehend the purpose of the study were excluded.

Demographic data along with comorbidities and duration of diabetes was obtained using a pre-structured data collection form. Metabolic measures like glycosylated hemoglobin (HbA1C), Fasting and Postprandial Plasma Glucose (FPG, PPPG), Low Density Lipoprotein (LDL) and Body Mass Index (BMI) was obtained at baseline. Outcomes were assessed using ACTT version 2 WHO Ordinal scales on day 10 and day 15 of symptoms onset. Association between COVID-19 outcome and glycemic statuses, BMI, ongoing anti diabetes therapy and concomitant use of statin and anti-platelet drugs were explored.

Data were statistically analyzed. Categorical data were presented as numbers and percentages, while continuous data were presented as mean ± standard deviation (SD). Measures of association was analyzed using Pearson's correlation coefficient. Different levels

were expressed at 95% confidence interval. A P value of less than 0.05 has been considered statistically significant. All statistical analyses for various measures were performed using various statistical software packages like Statistical Package for the Social Sciences (Windows version 21.0; SPSS Inc, Chicago, IL, USA) and Microsoft Excel.

RESULTS

A total of 248 diagnosed COVID-19 diabetic patients were included for the study. Male: female ratio for the included study population was 1.2:1, with 55.6% male predominance. The mean age was observed as 59.17 ± 14.45 years, with majority belonging to the age band of 50-60 years. The mean diabetes duration was noted to be 6.08 years. Comorbidities noted were hypertension (34.67%), followed by hypothyroidism (16.93%), chronic kidney disease (11.29%) etc. Metabolic measures such as HbA1C, FPG, PPPG, LDL and BMI were observed. For a total of 248 patients included, hospitalization was noted in 82.25% cases, while 20.97% cases needed mechanical ventilation. 27 deaths were noted. (Table 1)

Clinical Status Using ACTT Ordinal Scale was assessed on day 10 and day 15, and further outcomes were adjudged based on the status. (Table 2) Day 10

Table 1 — *Patient Characteristics*	
	Observed Value
Gender [n (%)]	
Male	138 (55.6%)
Female	110 (44.5%)
Age [n (%)]	
<40 years	3 (1.21%)
40 – 50 years	59 (23.79%)
51 – 60 years	98 (39.52%)
60 – 70 years	67 (27.01%)
>70 years	21 (8.46%)
Mean Age [Mean ± SD]	59.17 ± 14.45 (33 – 90)
Mean Diabetes Duration [Mean ± SD]	6.08 ± 5.37 (0 – 20)
Comorbidities [n (%)] :	
Chronic Kidney Disease	28 (11.29%)
Chronic Liver Disease	7 (2.8%)
Chronic Obstructive Pulmonary Disease	20 (8.1%)
Hypertension	86 (34.67%)
Hypothyroidism	42 (16.93%)
Ischaemic Heart Disease	15 (6.04%)
Obesity	15 (6.04%)
Mean Metabolic Indices [Mean ± SD] :	
HbA1C	7.44 ± 1.52 (5.6 – 11.2)
FPG	170.31 ± 80.06 (62 – 404)
PPPG	239.03 ± 111.53 (120 – 595)
LDL	110.61 ± 31.86 (62 – 188)
BMI	24.114 ± 3.61 (18.5 – 32.7)
Outcome [n (%)] :	
Hospitalizations	204 (82.25%)
Need for mechanical ventilation	52 (20.97%)
Death	27 (10.88%)

and day 15 clinical status was also associated with the baseline glycemic indices like HbA1C%, FPG, PPPG and LDL and BMI. Significant positive association was observed only for BMI (p=0.05) at Day 15, while rest association measures were non-significant (Table 3).

Drug Usage pattern suggested maximum use of metformin, followed by glimepiride and insulin. Other antidiabetic agents prescribed included canagliflozin, voglibose, linagliptin, sitagliptin, teneligliptin and vildagliptin (Table 4). However, negative correlation of COVID-19 outcomes with metformin usage, insulin

intake was observed though not statistically significant. No significant association was observed between COVID-19 outcomes and concomitant use of statin or antiplatelet drugs.

DISCUSSION

COVID-19 pandemic emerged infectious disease management as a global concern. Clinicians discovered that treating COVID-19 involved not just antimicrobials but also treatments for the disease's comorbidities. Glycaemic crisis has been common hindrance during COVID-19 infection or its management. The risk of hypoglycemia has been high in patients treated with sulfonylurea, meglitinides, and insulin. Interactions between these agents and other drugs like hydroxychloroquine used for COVID-19 treatment even increased the risk of hypoglycemia[5-7].

Also, COVID-19-associated hypothalamic-pituitary-adrenal axis hyperactivation, catecholamine surge, and cytokine circulation could cause hyperglycemia. Corticosteroids and vasopressors raised plasma glucose[3,8]. Studies suggest that acute stress like COVID-19, increases insulin resistance and decreases pancreatic reserve[9]. In COVID-19 patients, elevated glucagon, epinephrine, cortisol, and cytokines raise plasma glucose via increased hepatic glucose synthesis from glycogenolysis and reduced gluconeogenesis, or reduced insulin-mediated uptake. Furthermore, hyperglycemia causes endothelial dysfunction, catabolism, procoagulation, immunological dysfunction, sympathetic nervous system activation, platelet activation, acid–base disturbances, proinflammatory cytokine production, mitochondrial dysfunction, electrolyte, and fluid shift[3,8].

Elevated glucose levels directly promote SARS-CoV-2 replication in human monocytes, and glycolysis maintains replication by producing mitochondrial reactive oxygen species and activating hypoxia-inducible factor 1α[10]. Hyperglycemia may promote virus growth. Accordingly, hyperglycemia or a history of T1DM or T2DM independently predicted morbidity and death in COVID-19 subjects. Comorbid T2DM in mice infected with MERS-CoV caused a dysregulated immune response and significant lung pathology.[11] Thus, coexistence of T2DM increased SARS-CoV-2 infection severity and poor glycemic management predicts more hospitalizations, medicines, and death[12]. The present study was noted similar findings where poor glycemic control was associated with Day 10 and Day 15 outcome.

Initial investigations indicated increased severity of COVID-19, induced by SARS-CoV-2 infection, in diabetics. COVID-19 may potentially cause

Table 2 — Clinical Status Using ACTT Ordinal Scale		
	Percentage of Participants at Each Clinical Status	
Clinical Status Using ACTT Ordinal Scale	On Day 10	On Day 15
Not hospitalized, no limitations on activities	0%	11.1%
Not hospitalized, no limitations on activities	5.6%	11.1%
Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care	19.4%	8.3%
Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)	44.4%	30.6%
Hospitalized, requiring supplemental oxygen	5.6%	8.3%
Hospitalized, on non-invasive ventilation or high flow oxygen devices	2.8%	0%
Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	5.6%	0%
Death	16.7%	30.6%

Table 3 — Association of Clinical Status with Metabolic Indices				
	Day 10 Clinical Status		Day 15 Clinical Status	
	Pearson's Correlation Coefficient	P value	Pearson's Correlation Coefficient	P value
HbA1C	0.099	0.566	- 0.182	0.289
FPG	- 0.134	0.437	- 0.110	0.523
PPPG	- 0.194	0.257	- 0.116	0.502
LDL	0.097	0.573	0.266	0.117
BMI	0.125	0.473	0.374	0.027

Table 4 — Drug Usage Pattern Observed	
	Frequency (%)
Metformin	234 (94.35%)
Canagliflozin	14 (5.64%)
Glimepiride	97 (39.11%)
Voglibose	28 (11.29%)
Insulin	69 (27.82%)
Linagliptin	21 (8.47%)
Sitagliptin	16 (6.45%)
Teneligliptin	27 (10.88%)
Vildagliptin	42 (16.93%)
Statin	103 (41.53%)
Antiplatelets	35 (14.11%)

hyperglycemia. Hyperglycemia and other risk factors may modify immunological and inflammatory responses, predisposing individuals to severe COVID-19 and perhaps fatal results. The major entrance receptor for SARS-CoV-2 is ACE2, part of the Renin–Angiotensin–Aldosterone System (RAAS). DPP4 may also bind. Preliminary studies demonstrate that glucose-lowering DPP4 inhibitors do not affect SARS-CoV-2 susceptibility[13]. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are not indicated for COVID-19 patients due to their pharmacological properties. Acute glycaemia is best managed with insulin. In our study we could not found any significant association between glucose lowering agent usage. It could be due to small sample size and as this study was not longitudinal, which exists as a limitation of the study.

CONCLUSION

During the COVID-19, tight glycemic control and management of cardiovascular risk factors are imperative for patients with T2DM. Co-existence of COVID-19 and T2DM can further worsen the clinical outcomes, hence careful management approaches are warranted.

Source of Support : Nil
Conflict of Interest : None Declared.

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