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NEW ONSET DIABETES MELLITUS IN SECOND WAVE OF COVID -19 PATIENTS IN NORTH INDIA

Diabetology

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ABSTRACT

Background: Emergence of new diabetes mellitus cases, after infection with SARS Co-V2 is a serious concern. Understanding them and then following up these cases can enrich our knowledge about the etiopathogenesis of diabetes mellitus, and the diabetogenicity of these viral infections.
Observation: We had a series of adult Covid 19 cases in our hospitals in north India, during the early summer 2021. They did not have prediabetes or any predilection to develop diabetes. On admission, they had high blood sugar and needed insulin. After discharge from hospital, they needed insulin or oral antidiabetic drugs. Eight weeks into follow up, these cases still needed antidiabetic medicines.
Methods: Observational prospective study. Analysis of the past medical history, and comparison with the acute covid and post covid illness.
Results: The analysis of these cases shows that the SARS CoV2 infection results in diabetogenic changes leading to new onset diabetes.
Conclusion: Diagnosis of new onset diabetes must be kept in mind with every case of SARS CoV-2 infection, even after full recovery from acute covid -19.

KEYWORDS

SARS-CoV-2. Covid -19. Diabetes mellitus. HbA1c. Glycemic control. New-onset diabetes. ACE 2 receptors. Beta cell injury.

INTRODUCTION

Severe acute respiratory syndrome corona virus -2 (SARS- CoV-2) infections have a wide spectrum of presentations. It ranges from asymptomatic infections with spontaneous recovery, to severe illness. There have been presentations of severe and critical illness of Covid-19, associated with acute viral pneumonia, requiring oxygen support, often with assisted mechanical ventilation.[1] There have been 4 million deaths and 185 million cases already reported worldwide and 4.06 lakh deaths and 30.8 million cases in India, since the first case was reported from Wuhan. [2,3] As the new variants of this virus emerge at regular intervals, its varying levels of infectivity and changing patterns of virulence pose challenges to the healthcare system. The second wave of covid-19 in India, in the early summer 2021, has raised more serious concerns about the ability of this infection to trigger the glucogenic machinery in covid patients, leading to new onset diabetes mellitus. [4,5] Experts opined that it could be due to existing prediabetes state, undiagnosed diabetes, steroid induced diabetes, or stress induced diabetes mellitus. Damage to beta cells in the pancreas and its impaired function and/or development of insulin resistance (IR) are two probable factors for these new onset diabetes cases.[6] Damage to beta cells seems facilitated through increased viral entry through ACE2 receptors.[7] It is also not yet clear whether this diabetogenic feature of covid 19 in few cases, leads to T2DM, T1D or DKA, in isolation or with overlap of one type on the other. It shall take longer period of observations from multiple centres, to arrive at a conclusion.

SCIENTIFIC BASIS

Pancreatic beta cells have high levels of ACE2 receptors Viral entry into the islet cells containing beta cells of pancreas is facilitated through these receptors.[8] These viruses are supposed to cause damage to the islet cells in pancreas, and cause downregulation of ACE2 receptors leading to increased angiotensin levels, and impair the insulin secretion.[9] It could also be a systemic response of acute respiratory failure, through harmful immune response. Direct cytopathic effect of SARS CoV2 replication has also been linked to this diabetogenicity Pancreatic tissue on autopsy of a covid 19 patient detected SARS CoV2 viral infiltration in the beta cells of all patients.[10] Raised blood sugar levels in the cases of covid 19 have been linked to increased morbidity and mortality. [11]

METHODOLOGY

Observational prospective study. These cases were selected from our centres from North India, during the peak of second wave of Covid 19 in India, i.e., in the second fortnight of April 2021.

EXCLUSION CRITERIA:

Known cases of prediabetes, and a first degree relative of a known case of diabetes mellitus. Any one on steroid drugs for more than a week duration.

INCLUSION CRITERIA:

On admission, random blood sugar levels >250 mg/dL, HbA1c > 6.5%, who on admission needed insulin, and the ones who even after discharge from covid care centre, continued to be on insulin or oral anti diabetic medicines.

THE CASES

Case 1

Presentation:
A 33- year -old male presents with high grade fever, dry cough, body ache, malaise and fatigue, of 4 days duration. His rTPCR test for SARS CoV-2 virus is reported positive today.

On examination: Alert, temperature 100.2 F, sPO2 (on room air) 92%, RR 22/min, pulse 112 /m, BP 130/84 mm Hg. Chest: scattered wheeze. BMI 24 kg/m^2.

Has received dexamethasone, ivermectin and azithromycin. He has been taking budesonide inhalation for chronic bronchial asthma. Not vaccinated for SARS CoV2 infection.

No history of prediabetes and no first-degree relative a diabetic.
His routine health check done 2 months ago had these relevant findings: HbA1c 5.3, FPG 88 mg/dL, PPPG 140 mg/dL, Triglycerides 145 mg/dL.

Admission:
Admitted with provisional diagnosis of Covid 19 with new onset diabetes and DKA.

Investigations: Leucocytosis with relative lymphopenia, RBS 302 mg/dL, urine ketone positive, eGFR: 98. Chest x-ray findings: with increased broncho vascular markings & without any focal lesion.

Insulin was needed for the management. Insulin requirements- day1: 20 units, day 2: 46 units, day 3: 56 units, day 4: 56 units, day 5: 58 units, day 6: 56 units (please see chart: 1). On the seventh day, patient was discharged with the advice of NPH Insulin 24 units in morning & 16 units in the evening.

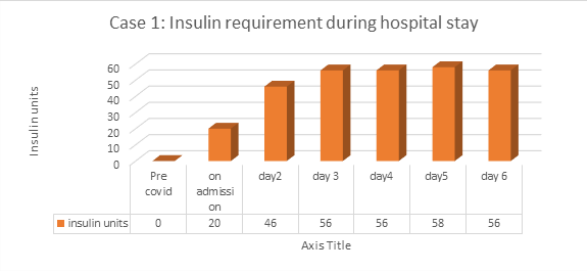

Chart 1: Insulin requirement during hospital stay- Case 1

Review after 1 week:
Asymptomatic. HbA1c 7.4, FPG 114 mg/dL, PPPG 202 mg/dL, Triglycerides 164 mg/dL, eGFR 96, urine sugar & ketone - nil. He is put on glargine insulin 16 units before supper, and glimepiride 2mg with metformin 1000 mg daily, in two divided doses.

After 6 weeks:
Asymptomatic. HbA1c 6.3, FPG 98, PPPG 168, Triglyceride154 mg/dL, eGFR 90, urine sugar & ketone -nil, c- peptide levels normal. Insulin stopped, and put on glimepiride 2 mg and metformin 2000 mg daily, in two divided doses.

Case 2
Presentation:
A 54 - year- old male, presents to the Accidents & Emergency at 11 PM; with complaints of increased breathlessness since last 4 hours. He has dry cough, sore throat, fatigue and body ache of 5 days duration. His rTPCR for SARS COV-2 is reported positive 2 days ago, He also had low grade fever one week ago that lasted for 3 days. Now afebrile. No history of steroids intake or intravenous dextrose infusions.

He takes telmisartan 40 mg twice daily for hypertension.

On examination: alert patient, sPO2 (at room temperature) 82%, RR 26/ m, pulse 110/m, BP 142/88 mm of Hg, temperature 98.2 F, chest with occasional rhonchi. BMI 22.7 kg/m^2.

No history of prediabetes and no first degree relative a diabetic.
His routine medical check done 3 months ago, had these relevant findings: HbA1c 5.1%, FPG 83 mg/dL, PPPG 138 mg/dL, urine sugar nil, albumin +, triglycerides 154 mg/dL.

Admission:
Admitted with a provisional diagnosis of Covid 19, acute viral pneumonia with respiratory distress and new onset diabetes mellitus.

Investigations: Leucocytosis with relative lymphopenia, RBS 423 mg/dL, HbA1c: 8.1, urine sugar & ketones -negative, eGFR: 88, EKG: sinus tachycardia, no ST – T changes. Chest x-ray: increased broncho vascular markings, no focal parenchymal lesion.

He was treated with NIV oxygen supplementation, ceftriaxone and insulin infusion. After 3 days, his oxygen saturation (on room air) improved to 96 %, and the 6MWT was negative. Insulin requirements: day1: 18 units, day 2: 34 units, day 3: 46 units, day 4: 52 units, day 5: 52 units, day 6: 52 units, day 7: 52 units (please see chart-2). He was discharged on NPH Insulin 20 units before breakfast and 14 units before supper.

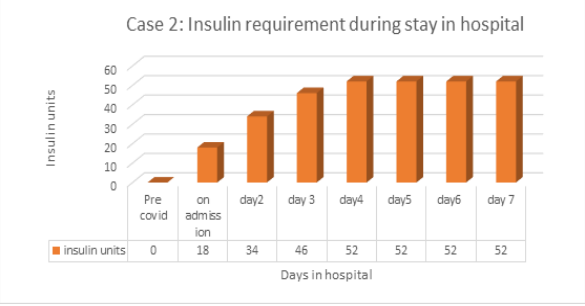

Chart 2: Insulin requirement during hospital stay- Case 2

Review after one week:
Asymptomatic. FPG 106 mg/dL, PPPG 234 mg/dL, eGFR 90, NPH insulin was discontinued, and he was put on linagliptin 5 mg with 500 mg metformin with breakfast, and glargine insulin 20 units before supper.

After 6 weeks:
Asymptomatic. HbA1c 7.4, FPG -98 mg/dL, PPPG- 188 mg/dL, eGFR 88. c- peptide levels normal. Insulin glargine was discontinued, and he was put on linagliptin 5 mg once daily & metformin 850 mg twice daily.

Case 3
Presentation:
A 53 – year- old female presents in the OPD, with the complaints of fever, dry cough and fatigue of 5 days duration. She has rTPCR positive for SARS Co-V2. She has HRCT thorax reports showing ground glass appearance bilaterally with CT severity score of 10/25. She has taken prednisolone, azithromycin, ivermectin and zinc tablets. She is on thyroxine 125 mcg and cilnidipine 10 mg daily.

On examination: Alert patient, sPO2 (at room temperature) 88 %, RR 22/ m, pulse 110/m, BP 142/88 mm of Hg, temperature 98.2 F, chest with occasional rhonchi. BMI 26.7 kg/m^2.

No history of prediabetes and no first degree relative a diabetic. Routine medical check -up done 6 weeks ago, she had HbA1c 4.9 %, FPG 88 mg/dL, PPPG 127 mg/dL, urine sugar & ketones - nil, triglycerides164 mg/dL.

Admission:
She was admitted with provisional diagnosis of covid -19 with new onset diabetes mellitus, hypothyroidism & hypertension.

Investigations: Leucocytosis with relative lymphopenia, RBS 382 mg/dL, HbA1c: 6.8, urine sugar & ketones -negative, eGFR: 88, EKG: sinus tachycardia, no ST – T changes. Chest x-ray: increased broncho vascular markings, no focal parenchymal lesion.

Steroids were continued for 3 more days. Insulin was needed. Insulin requirements: day1: 10 units, day 2: 24 units, day 3: 38 units, day 4: 44 units, day 5: 46 units, day 6: 46 units, day 7: 42 units (please see chart-3). After 7 days, she was discharged on basal- bolus insulin regime: glargine insulin 20 units before supper and lispro insulin 16 U-16 U-12 U.

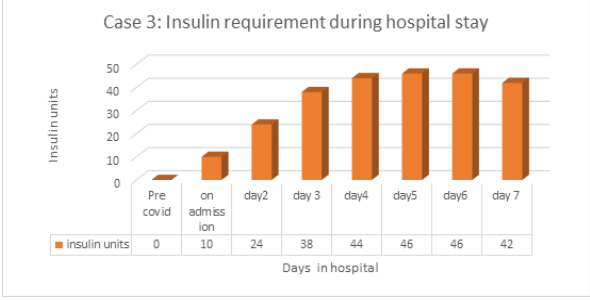

Chart 3: Insulin requirement during hospital stay- Case 3

1 week later:
Asymptomatic. FPG 102 mg/dL, PPPG 178 mg/dL. She was put on 16 units glargine and metformin 850 mg twice daily.

6 weeks later:
Asymptomatic. HbA1c 6.5 %. FPG 92 mg/dL, PPPG 164 mg/dL, c-peptide levels low, eGFR 70, TFT normal.

She was continued on glargine insulin 10 units, before supper, and linagliptin 5 mg with metformin 1000 mg daily.

Case 4
Presentation:
A 41 – year- old female, brought to the A & E at 2 AM, with complaints of severe pain abdomen of 6 hours duration. She had nausea and vomiting for 12 hours. No loose motions or distension of abdomen; passing flatus. Has had fever for 5 days, that still continues. Her rTPCR for SARS COV-2 is positive. She was taking azithromycin, doxycycline, dexamethasone and ascorbic acid.

On examination: alert patient, sPO2 (at room temperature) 91%, RR 18 / m, pulse 108 /m, BP 132 / 80 mm of Hg, temperature 98.2 F. Abdomen: soft, tenderness in epigastrium & right hypochondrium, bowel sounds normal. BMI 22.8 kg/m^2.

No history of prediabetes & none of her first -degree relatives are diabetic. No h/o alcohol intake or smoking.

On routine medical check- up done 2 months ago, she had these relevant findings: HbA1c 5.1 %, FPG 78 mg/dL, PPPG 138 mg/dL, urine sugar nil, triglycerides 152 mg/dL, LFT & KFT normal. Sonography of whole abdomen was normal. EKG was normal.

Admission:
Admitted with a provisional diagnosis of Covid -19, acute pancreatitis & new onset diabetes mellitus.

Investigation: Raised serum lipase & amylase, leucocytosis, d dimer levels raised 6- fold normal, RBS 308 mg/dL. Xray abdomen: No free fluid or gas under the diaphragm. Sonography abdomen showed fatty liver grade 1, no calculi in gall bladder or its ducts, no calculi in genitourinary tract. EKG normal

She was given intravenous fluids, pantoprazole, enoxaparin, ondansetron and insulin infusion. Pain abdomen and vomiting subsided within 24 hours of admission. Insulin requirements: day1: 08 units, day 2: 30 units, day 3: 42 units, day 4: 42 units, day 5: 42 units, day 6: 40 units, day 7: 36 units (please see chart 4). After 7 days, she was discharged on NPH Insulin 30 units &18 units. She was also put on apixaban, pantoprazole, and pancreatic enzymes supplements.

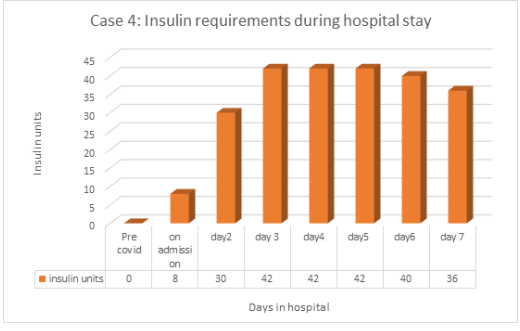

Chart 4: Insulin requirement during hospital stay- Case 4

One week later:
Asymptomatic. FPG was 98 mg/dL, PPPG 167 mg/dL, eGFR 82, d-dimer marginally raised, platelets, LFT and pancreatic enzymes normal. USG whole abdomen was normal. NPH insulin was continued.

After 6 weeks:
Asymptomatic.HbA1c 6.4 %, FPG 90 mg/dL, PPPG 136 mg/dL, eGFR 82, In serum- uric acid, calcium, pancreatic enzymes were normal. LFT, USG, CXR & EKG were normal. C-peptide levels normal. Insulin was discontinued, and she was put on glimepiride 2 mg and metformin 1000 mg daily.

Case 5
Presentation:
A 74 -year male patient presented with the complaints of fever of one week duration. Increased sputum and increased breathlessness, sputum white. No chest pain, wheeze or haemoptysis. His rTPCR for SARS COV-2 is positive

Has COPD and hypertension. Controlled well on ipratropium & budesonide inhalation, and amlodipine 5 mg daily.

On examination: alert patient, sPO2 (at room temperature) 86 %, RR 24 / m, pulse 118 /m, BP 154 / 94 mm Hg, temperature 99.2 F. Chest with scattered wheeze. BMI 22.1 kg/m^2.

Chest x-ray: emphysematous chest. HRCT thorax shows ground glass appearance in lung fields, CT severity score 12/25. EKG: sinus tachycardia, p - pulmonale, no significant features of ischemia or arrhythmia. RBS 432 mg/dL, leucocytosis, eGFR 72. HbA1c 6.9 %, urine sugar ++, urine ketones nil.

No history of prediabetes and no first degree relative a diabetic. Routine medical check -up done 10 weeks ago, he had HbA1c 5.2 %, FPG 88 mg/dL, PPPG 127 mg/dL, urine sugar & ketones - nil, triglycerides164 mg/dL, eGFR 74.

Admission:
Admitted with provisional diagnosis of covid-19 with new onset diabetes mellitus, exacerbation of COPD with acute bronchopneumonia, and hypertension.

He was treated with NIV oxygen supplementation, amoxycillin & clavulanic acid, nebulization with budesonide & ipratropium and insulin. Insulin requirements: day1: 12 units, day 2: 60 units, day 3: 68 units, day 4: 78 units, day 5: 64 units, day 6: 64 units, day 7: 64 units (please see chart 5). Discharged on, the day 8, with advice of glargine insulin 10 units with supper, lispro insulin 16 U- 16 U- 10 U, cilnidipine 10 mg, and nebulization with ipratropium & budesonide.

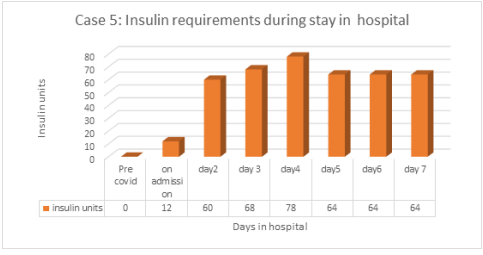

Chart 5: Insulin requirement during hospital stay- Case 5

1 week later:
Breathlessness and cough better. sPO2 (on room air) 94 %, the 6MWT positive. Chest: occasional rhonchi. Afebrile, BP 132/ 88 mm of Hg, pulse 102/ m. FPG 112 mg/dL, PPPG 204 mg/dL, urine: no sugar/ketone. Chest x-ray: better.

He was put on NPH Insulin 24 U & 16 U. Nebulization continued. Levofloxacin was prescribed for 10 days.

6 weeks later:
Better. sPO2 96 %, the 6MWT negative. CXR better and HRCT thorax normal. Hb A1c 6.3, FPG 104 mg/dL, PPPG 162 mg/dL. Continued on same doses of Insulin.

DISCUSSION
SARS CoV2 virus infection makes it difficult to control raised blood sugar levels in diabetes. [12,13] It is also found to trigger glucogenic factors[14] There have been an occasional case reported where diabetes mellitus has surfaced during acute illness of covid 19 and even after recovery from covid 19.[15,16] The possibilities are that it could be that it was a case of undetected diabetes, a prediabetes, stress or steroid induced diabetes. Or the patient may have had genetic predisposing factors. In the cases presented here, all the above-mentioned factors were ruled out, and even after 7 weeks of discharge from covid care hospital, the patients needed antidiabetic drugs for adequate control of blood sugar levels. Their old medical records within 3 months of acute covid 19 illness, rule out a prediabetic condition. In a comparative study of the HbA1c levels of all these five patients, it was found that there was rise in HbA1c after the coronavirus's infections (please see chart-6). All these patients needed insulin infusion to control plasma sugar, and all of them needed insulin or oral antidiabetic drugs for the control of diabetes mellitus.Case 4 had injury to the pancreas affecting its exocrine functions also, that points towards the pathology of injury to the pancreas during SARS CoV2 infections. Case 1 had DKA. DKA has been reported to be one of the ways of presentation of the new onset diabetes mellitus in covid 19.[17]

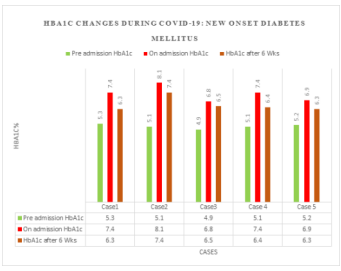

Chart 6: Glycosylated haemoglobin (HbA1c) in all the cases

Limitations

This study has few limitations, which include observational prospective study design of a disease entity, which is of recent occurrence. These cases shall be on a long term follow up to see whether this post covid new onset diabetes is a reversible phenomenon or not. If the beta cell dysfunction is due to the cytokines and other factors, and in due course of time, the offending factors are removed by the immunosurveillance and other mechanisms, then this may reverse. Or if the beta cell dysfunction goes on unabetted, and if along with development of Insulin resistance, then these cases may even worsen, in terms of glycaemic control.

CONCLUSION

New onset diabetes mellitus is a serious ailment occurring in the patients during and after having recovered from the acute illness of covid -19. As it is, in any case of existing T2DM one finds it difficult to control the levels of blood sugar during acute illness of covid -19. The increasing incidence of new onset diabetes associated with covid -19, cautions the healthcare providers, as well as the population at risk, to be vigilant about the glycaemic control in post covid period.

INFORMED CONSENT

A written informed consent to publish the information about the clinical condition and the relevant reports, was obtained from the patient.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Abbreviations:

Type 2 diabetes mellitus (T2DM). Type 1 Diabetes (T1D). Fasting plasma glucose (FPG). Postprandial plasma glucose (PPPG). Diabetic ketoacidosis (DKA). Liver function tests (LFT). Thyroid function tests (TFT). Chest x ray P A View (CXRPAV). Ultrasonography (USG). Electrocardiogram (EKG). Chronic obstructive pulmonary diseases (COPD). High resolution computed tomography (HRCT). Angiotensin-converting enzyme 2 (ACE2). Coronavirus disease- 19 (Covid -19). Insulin resistance (IR). Saturation of peripheral oxygen (sPO2). Body mass index (BMI). Estimated glomerular filtration rate (eGFR). Six- minute walk test (6MWT). Reverse transcription polymerase chain reaction (rTPCR).

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