

EFFECTIVE RESPONSE TO DPP-4 INHIBITORS IN PATIENTS OF COVID – 19 TRIGGERED UNCONTROLLED TYPE 2 DM – A CASE REPORT

ABSTRACT

INTRODUCTION: A bidirectional relationship exists between the COVID-19 diagnosed & recovered patient and Type 2 Diabetes Mellitus. As per the various articles available in the public domain, it has been proved that entry of COVID-19 virus can lead to a series of pathological changes in a patient's body which may lead to the development of insulin resistance and damage to the pancreas.

The patient in our case was a COVID-19 survivor which was diagnosed with type 2 DM during the treatment. The patient was started with the Glargine insulin when she was undergoing her treatment in the hospital for COVID-19 symptoms. Her fasting and postprandial blood sugar level was controlled with the insulin. After her discharge, she was started with the Metformin 500 mg twice a day but her blood sugar was not controlled with the Metformin monotherapy, so we started with the triple drug combination Metformin + Glimepiride + Pioglitazone. After 1 month of follow-up, it was seen that the blood sugar level was not controlled, so the Pioglitazone was replaced with the DPP-4 inhibitor drug Vildagliptin and again the patient was asked to come for follow-up after 15 days, it was seen in this follow-up that the patient's blood sugar was dramatically controlled.

CONCLUSION: COVID-19 triggered Type 2 DM is the result of cytokine storm development during the disease. Metformin and DPP-4 inhibitors reduce the insulin resistance in type 2 diabetes patients and help to achieve the euglycemic goal of the patient.

KEY WORDS: DPP-4 inhibitors, Uncontrolled diabetes, COVID-19, Vildagliptin, Triggered Type 2 DM

INTRODUCTION

The SARS-CoV-2, that causes coronavirus disease (COVID-19), first time reported in December 2019 in Wuhan city, China, and has unfurl worldwide. COVID-19 is a Ribonucleic Acid with single strand. The infection is spread by droplet infection. The respiratory system is the 1st to get affected, the virus then releases cytokine storm which acts on various organs and affect the metabolic process. Diabetes mellitus and Cardiac related

diseases are the most common liable factor for raised coronavirus infection, the disease severity and worst disease outcomes, including increased chances of mortality.¹ COVID-19-associated diabetes isn't the result of a single occasion but is a combination of illness vulnerability related with persistent ailment and COVID-19-specific cause affecting the body metabolism. It is not yet clear that a post COVID – 19 diabetes is associated with long lasting β -cell damage and responsible for uncontrolled diabetes. A two-way relationship exists between Covid-19 and diabetes, on the one side, diabetes is related with an expanded chance of serious Covid-19, while on the flip side, new-onset diabetes and serious metabolic complications of pre-existing diabetes, counting diabetic ketoacidosis and hyperosmolarity for which outstandingly excessive dosages of insulin are justified, have been noticed in patients with Covid-19.^{2, 3, 4} The increased in the levels of Tumour necrosis factor and Interleukin 6 are the result of COVID -19 inflammation and cytokine storm.⁵

CASE REPORT

Patient Information: A 48-year-old female patient survivor of the COVID – 19 disease came to the OPD with the complaint of increased hunger, increased thirst and burning sensation in both the feet. Her signs/symptoms and diagnostic test were suggestive of COVID – 19 disease, so she was admitted to the hospital. During her stay in the hospital her CT score was 6, C Reactive Protein 6.84 mg /dl, D Dimer 107.4ng/dl, serum LDH 1050.5 IU/L and serum ferritin 242.9 ng/ml, her fasting and post meal blood glucose level was 280 mg /dl and 390 mg/dl, the patient was treated in the hospital according to the COVID – 19 protocol. She was started with the insulin glargine 10 units, and her fasting and postprandial blood sugar level got controlled. After discharged from the hospital, she was started with the Oral antidiabetic drugs Metformin 500 mg twice a day. The patient was never previously diagnosed with the Type 1 Diabetes Mellitus before getting infected with Corona Virus.

Clinical Findings: When the patient came to our OPD her fasting blood glucose level was 334 mg/dl and the postprandial blood sugar level was 409 mg /dl and her HbA1c was 15.90%.

Therapeutic Intervention: The patient was not ready to restart with the insulin therapy because of lack of assistance at her home, The patient was started with Tab Metformin 500 mg two times in a day, Tab Glimpiride 1 mg twice a day and Tab Pioglitazone 15 mg once in a day. The burning sensation in the foot were managed separately and the patient didn't complaint about it in the subsequent visits. She was asked to repeat fasting and postprandial blood sugar level after 1 month. After 1 month of treatment the patients fasting and postprandial blood sugar level didn't improve. The patient was then continued with Metformin and Glimpiride

with same dose and frequency and Tablet Pioglitazone was replaced with Tablet Vildagliptin 50 mg twice a day.

Follow – up and Outcomes: After 15 days of treatment the patients fasting and postprandial blood glucose level shows improvement, her fasting blood sugar level was 188 mg/dl and her postprandial blood glucose level was 230 milligram per decilitre. The patient was asked to continue with the drugs and was asked for follow up after 2 months. The patient was instructed for self-monitoring of plasma blood sugar level with glucometer.

After 3 months the patient came with the reports of fasting, postprandial and HbA1C. The fasting blood sugar was 160 milligram per decilitre and the postprandial blood sugar level was 215 milligram per decilitre. The HbA1C level was 9.4 %. The same drugs and the dose was continued and the patient was asked to monitor the blood sugar level at home with the help of glucometer. The patient continued the same medicine and again came for the follow-up after 4 months with the Fasting Blood Sugar Level – 132.4 mg /dl and Postprandial Blood Sugar Level – 168.3 mg /dl. The HbA1C was 7.14%.

Initially the triple drug combination regime of Metformin + Glimepiride + Pioglitazone has failed to reduce the blood sugar level but after replacing the Pioglitazone with Vildagliptin the same regime has dramatically reduced the blood sugar level.

DISCUSSION

Diabetes is the commonest non transmissible metabolic disorder, according to IDF total 463 million patients worldwide are suffering from diabetes, of these 77 million patients are present in India.⁶ A bidirectional relationship has been observed between COVID -19 and Type 2 DM. On one side Diabetes increased the COVID -19 risk of infection and on the other side COVID – 19 has resulted in the new diabetes onset and complications like diabetic ketoacidosis and hyperosmolarity like conditions in pre-existing diabetes patients.^{7, 8, 9} The COVID – 19 virus enters through ACE 2 receptor inside the human body. The virus enters inside the human body by binding to the spike protein (S) of the virus. After entering into the alveolar epithelial cells, the viruses undergo replication to produce more structural protein of the coronavirus. The viral pneumocytes releases cytokines and inflammatory markers like interleukins (IL-1, IL-6, IL-8, IL-120 and IL-12), Tumour Necrosis Factor(TNF- α), Interferons (IFN- λ and IFN- β).¹⁰ The ACE 2 receptors also exists in the organs and tissues like lungs, liver, brain, placenta and pancreas. Compared to other organs these receptors are predominantly present in the pancreas.¹¹

The entry of SARS CoV 2 virus causes dysregulation of ACE 2 receptors leading to upregulation of Angiotensin II which further induces oxidative stress by NADPH oxidase induction and damages the β cells of the pancreas.¹² The COVID -19 induced cytokine storm causes release of Tumour Necrosis Factor and Interleukin 6 which are responsible for peripheral insulin resistance.^{13, 14}

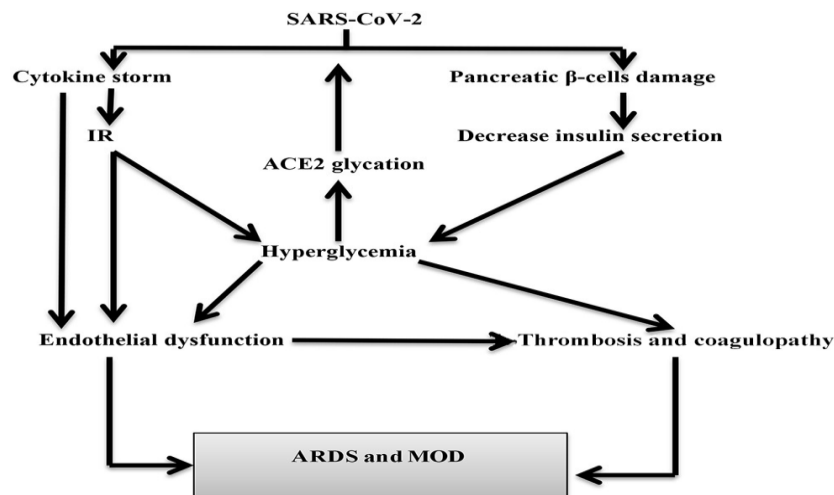


Fig 1: Mechanism of COVID – 19 infections triggered Hyperglycaemia

IR – Insulin Resistance, ACE 2 – Angiotensin convertase enzyme,

Oral Drugs used for the management of Type – 2 Diabetes Mellitus

Metformin is an Oral drug use for the treatment of type 2 diabetes mellitus. Metformin activates AMP dependent protein kinase and improves the insulin resistance. Metformin also inhibits the synthesis and release of C reactive protein, Interleukin 1 β and IL 6.¹⁵ Glucagon like peptide and gastric inhibitory peptide are the incretins which release insulin. In the presence of Dipeptidyl peptidase-4 Inhibitor (DPP4) they get metabolize. DPP4 inhibitors drugs prevents the inactivation of Glucagon Like Peptide 1 (GLP) by inhibiting the DPP4 enzyme and there by enhance insulin secretion.¹⁶ In addition to this mechanism DPP 4 inhibitors exhibits anti-inflammatory effects by activating the anti-inflammatory cytokines, and the macrophage polarizations, and also by inhibiting the pro-inflammatory cytokines.¹⁷

In the above reported case, the patient was diagnosed with type 2 DM after she was hospitalized for the treatment of COVID – 19 infection. At the time of the first visit, the patient was started with the combination of Metformin + Glimepiride + Pioglitazone. After one month of follow-up the patient had uncontrolled diabetes so the tablet Pioglitazone was replaced with Vildagliptin. After 15 days the patients fasting and blood sugar level investigated and it was seen that the combination of Metformin + Glimepiride + Vildagliptin reduces the fasting and the postprandial glucose level and helped to achieve the

euglycemic goal of the patient. In subsequent visits, it was seen that the premeal and post meal blood glucose were controlled and also the HbA1c value was reduced from 15 % to 9 % and again to 7 % in the subsequent visits. The COVID -19 triggered type 2 DM is having an inflammatory pathophysiology which is responsible for decreased secretions of insulin and development of insulin resistance. Metformin and Vildagliptin both have an anti-inflammatory effect, which are having a very critical role in the COVID – 19 triggered type 2 DM. Both the drugs if given to the patient of COVID -19 triggered type 2 DM can reduce the blood sugar level and help to attend the euglycemic stage.

CONCLUSION

COVID - 19 pandemic has turned into the greatest health challenges in the history of mankind. COVID – 19 causes the release of cytokine storm, which leads to hazardous effects on various organs including the pancreas. Our patient from the above scenario was not suffering from any signs and symptoms of diabetes before she suffered from COVID – 19 infection. This proves there must be some relationship between the COVID – 19 and the type 2 diabetes mellitus. Rise in the blood sugar level in SARS corona infection is again liable for the worst prognosis of the disease or even death of the patients. Antidiabetic drugs plays a very crucial role during COVID – 19 triggered type 2 diabetes mellitus. They may not exactly reverse the pathology of the disease but help in reducing the resistance of the insulin and also prevents the pancreas further damage by activation of anti-inflammatory cytokines. DPP4 inhibitors along with Metformin have a very critical role in the control of type two diabetes mellitus in COVID – 19 survivors.

Consent Disclaimer:

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

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