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## Current Treatment Trends in T2DM and Impact of COVID-19 among T2DM Patients: A Review

	
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### ABSTRACT

Diabetes does not come alone; it comes with a number of co-existing illnesses which includes blindness, kidney failure, heart disease and neuropathy. They may share similar risk factors or may be a complication of it. The therapy given to these patients and the goal of this therapy is to control the blood sugar level. It is personalized for the individual patient on the basis of his body's demand and other co-existing illnesses. According to WHO, Diabetes is one of the leading cause of death all over the world. Changing lifestyle of people in developing countries like India has tremendously increased the statistical figure of chronic diseases like diabetes mellitus. The motive behind the DUE studies is to optimize the therapy and promote appropriate use of drugs up to the standards in the hospital setting. Despite of so many anti-diabetic agents in the market, metformin is still recommended as first choice of drug in the treatment. The most common combinational therapy given to diabetics was glimepiride and metformin. The physician's decision lies on various factors like the Pharmaceutical resources, cost of the medicine, his personal attribute, physiological state of the patient and many more. Various newer agents are being developed by the pharmaceutical companies for more efficient treatment in different situations. The newer agents include Tenzinogliptin, Linagliptin, Exenatide, etc. Regular treatment is the key feature related to the effectiveness of the therapy in the patients. But an eye should be kept on the ADRs from these medications for more safety data. For example if metformin was used in a dose of more than 1000mg/day it results in Metformin-induced dyspepsia. For the estimation of risk factors to ensure maximum benefits of the treatment, assessment of ADR is important. In COVID-19 infection, diabetic patients are at risk for their hospitalization and mortality. The challenge is the treatment of hyperglycemia during infection and the infections further leads to loss of glycemic control. More frequent monitoring of blood glucose level and continuous alteration in the therapy as per the requirements should be done.

## 1 INTRODUCTION

The use of drugs is a very complex process and its inappropriate use may result in increased cost of medical care, adverse effects and even patient's mortality. DUE or DU studies are designed to review the drug use or prescribing trends to develop criteria and standards for optimal drug use, promote appropriate use of drugs and provide feedback to the clinician.<sup>[1]</sup> Diabetes mellitus is a cluster of metabolic disorders which can be categorized by increased level of blood sugar. Chronic complications, microvascular as well as macrovascular disorders are the results of abnormalities in carbohydrates and fat metabolism in diabetic patients. Prevention of a diabetic patient from complications and enhancing the quality of life are the major challenges for clinicians.<sup>2</sup>

Good glycemic control along with the management of co-morbidities such as hyperlipidemia and hypertension, and prevention of long-term complications, are the keystone for the management of diabetes mellitus. The changing lifestyle of people in developing countries like India has tremendously increased the statistical figure of chronic diseases like diabetes mellitus.<sup>[3,4]</sup> As per the International Diabetes Federation by the year 2035, the number of people suffering from diabetes globally will reach 592 million from 387 million. The prevalence data of diabetes in India in year 2000 was 31.7 million which has reached to 65.1 million in year 2013 and by the year 2030, it will reach to 79.4 million.<sup>[5]</sup> The residence of co-morbidities in a diabetic patient is very common because of common risk factors for example dyslipidemia, obesity, vascular inflammation and endothelial dysfunction. Patients having diabetes have higher risk of ESRD, cardiovascular complications and hypertension along with depression, thyroid gland diseases and COPD.<sup>[6]</sup> Hence management of these co-morbidities along with diabetes is a major concern.

Deciding the therapy for the patient is a tough task nowadays. One of the reasons for this is the increasing number of co-morbidities in the patient. The physicians are the stakeholders in such conditions in India. They decide the best drug suitable for the patient on the basis of various factors. The drug of choice should be safe, effective and budget friendly to the patient. The physician's decision depends upon patient's requirement. This is also known as individualization or personalization of therapy.

Regular treatment is the key element related to the effectiveness of the therapy in patients with diabetes mellitus. The antidiabetic agents have different mechanisms of decreasing the blood sugar level. Besides, the patient's demographics, route of administration, glycaemic effect and adverse events of the antidiabetic drugs should be considered while deciding the pharmacotherapy of the diabetic patients. The fruitfulness of antihyperglycaemic therapy may be affected by various factors and continuity of treatment should be considered. [7]

ADR can be described as any response to a drug at normal doses used for prophylaxis, diagnosis, and modification of physiological functions or treatment of a disease which are unintended and toxic. It is obvious that adverse drug reactions can occur with the drug of any class. It can occur by a single dose or prolonged administration of drug or can be a result from combination of two or more drugs. [8]

It was observed that ADRs were mostly related to gastrointestinal and endocrine system. For the estimation of risk factors to ensure maximum benefits of the treatment, assessment of ADR is important. [9]

COVID-19 can be characterized by a dry cough, fever, fatigue and dyspnea (difficult or labored breathing), and majority of the symptoms will be minor. For a few people, this illness can progress to pneumonia which may further lead to multiorgan failure. People with diabetes have higher risk of COVID infection. The overall mortality related to cardiovascular disease is continuously declining among people with diabetes whereas on the other hand pneumonia has increasingly become an important cause of death in diabetes, with different contributing pathogens. Currently, it is unknown why people with diabetes, hypertension or other chronic diseases are more seriously affected by COVID-19. [10]

### **Evaluation of Anti Diabetic Drug Utilization in Hospitals**

Shekhar Mandal et al. observed during his study that the most prescribed drug to the patients was metformin either as monotherapy or in combination therapy. The inclination of the prescribers is more towards combination therapy (commonly metformin and glimepiride) specially two drug therapy. This was because monotherapy is mostly not sufficient for glycaemic control. Though adherence to the treatment guidelines was good but the prescribing practices need to be further improved. [11]

A prospective study by Thushara et al observed that patients having diabetes for less than 5 years can be treated by monotherapy but those having it for a longer time require combinational therapy. Besides insulin and metformin, drugs of class Sulfonyl Ureas are the most prescribed ones in combinational therapy. [12]

Another study by L. Sutharson has found that the patients are not having adequate knowledge about their therapy. Nearly 50% of the patients do not have sufficient information about their dosage schedule. The communication error is supposed to be the probable reason. Improving patient's knowledge by spending more time by the pharmacist while dispensing can improve the quality of the health care system.[13]

A prospective cross-sectional study by Khushali G Acharya et al has concluded that the compliance of the patient to the therapy can be improved by prescribing the oral medications rather than injections. In addition to this, the cost per prescription can be cut out by prescribing more generic preparations. [14]

A study carried out by Alti Aparna et al. in which it was noted that the age group which was most affected by diabetes were between 40-60 years. The combinational therapy is preferred more nowadays to control the FBS of the patients. [15]

The effectiveness of the treatment depends upon the prescriber's drug selection, patient's adherence to the prescription and the changes to the therapy done by the prescriber. Good adherence to the drug regimen can achieve good glycemic control. Hence, various steps should be taken to improve the adherence of the prescription. The monitoring of the patient's compliance to the therapy is done to get control over the blood sugar level. Certain actions should be taken to improve this compliance and hence for the better treatment of the patient with type 2 diabetes mellitus. As a whole the management should involve dietary changes, lifestyle modifications, and hypoglycaemic agents, monitoring for complications and treating co-morbidities.[16] The most common combinational therapy given to diabetics was glimepiride and metformin. In DUE studies the pattern of drug use is studied. [17]

A DUE study by Mandana Moradi et al. has drawn an inference that the maximum patients were treated with metformin when first diagnosed with diabetes. The co-morbidities which were most frequently found were hypertension and visual disablement. The ADRs which

were mostly reported were hypoglycaemic episodes and gastric upset associated with insulin and oral hypoglycaemic agents respectively. It was noted that educating patient to strictly following the dosage regimen along with lifestyle modifications and blood glucose monitoring may lead to effective management of diabetes.[18] A study by Tamoghna Maiti et al. concluded that the drug utilization evaluation studies should be done time to time on different patient population from different socio-economic background at different places. The drugs of class DPP4 inhibitors are more extensively used because there is no risk of hypoglycaemia by these drugs. [19]

As per a study done by Santusta Adhikari et al in Nepal, the minimization of the complications of diabetes is necessary which can be done by keeping strict control over the blood sugar level, rational drug preferences and early diagnosis. Cardiovascular complications are the most frequent among all the complications of diabetes. Poor glycaemic control mainly leads to complications. [20]

### **Treating Co-morbidities among Diabetic Patients**

Diabetic patients are having increasing rates of multiple lipid abnormalities. Up to sub-optimal lipid level, no lipid-modifying therapy is given to the patients. The patients who didn't have benefit from adjunctive treatment with niacin and fibrates, statins are prescribed. Diabetic patients are not treated up to ADA targets. Further, tailored lipid lowering therapy in diabetic patients need to be investigated to achieve the goal of therapy. [1]

About 30% of diabetic patients are having coronary artery disease. The various risk factors and metabolic disorders are the burden over patients with diabetes mellitus and acute myocardial infarction. The lipid profile assessment should be done with special priority in diabetic patients. The ineffective lipid lowering therapy in patients with diabetes may lead to developing AMI. 20% of diabetic patients with AMI were having atrial fibrillation. Hence, such patients require individualized treatment strategy because of previous revascularization. [2]

For patients with diabetes and heart failure, the most efficient therapy is glucose-lowering therapies with SGLT2 inhibitors. This leads to the elimination of glucose by kidney which can improve the myocardial function in obese patients with or without diabetes. Some evidences are there for metformin which resulted in decreased glucose production

endogenously and proved beneficial for patients with heart failure and diabetes. On the contrary, the agents which directly or indirectly increase the insulin level have no significant result in heart failure. [3]

The most favorable management for Diabetic Retinopathy for Diabetic Retinopathy is to control the systemic risk factors which prevent leading to visual complications. Despite the fact that Pan-retinal photocoagulation has been used for Proliferative Diabetic Retinopathy for years, recently anti-vascular endothelial growth factors are found as a valuable therapy for it. [4], another similar study, a systemic review done by Quresh Mohamed et al on treatment of diabetic retinopathy in which it was concluded that the risk of visual loss in patients with severe Diabetic Retinopathy and Macular edema can be reduced by Pan-retinal photocoagulation and focal retinal photocoagulation. Tight blood pressure and glycemic control are the main fundamentals in the prevention of Diabetic Retinopathy. [5]

The relation between diabetes and depression is bidirectional that is the depression lead to emergence of diabetes and conversely, diabetes could lead to depression as well. The pathophysiology of depression associated with diabetes is very complex and that's the reason why an effective treatment with negligible side effects is not available yet. However, it was seen that the drugs which are first drug of choice for depression aggravates the hyperglycemic conditions. [6]

By applying Piette and Kerr framework it was found that diabetic patients with different co-existing medical illness have different health care expenditure profiles. Diabetic patients with both concordant and discordant conditions and with clinically dominant conditions have higher cost of health care as compared to other diabetic patients. Such patients with multiple co-existing illnesses may require a tailored regimen for them. [7]

A comparative review study by Michael J. et al found that the JNC 8 committee has declared more strict BP recommendations in the patient groups with diabetes mellitus and CKD. Besides, JNC 8 promotes evidence based medicine which will enhance the role of expert's opinion. The management of hypertension in diabetic patients is done by individualization of the therapy. The guidelines help the physicians while clinical decision making which positively contributes to diabetic patient care and outcomes. [8]

The obesity management in diabetic patient is very helpful in its management as it reduces the blood sugar level and reduces the demand of glucose lowering medications. Some studies have found that more dietary restrictions and very low calorie food can reduce A1C and FBS to normal levels. The weight loss therapy, including diet, behavioral and pharmacologic interventions treats hyperglycemia in type 2 diabetes mellitus. The prescribers should keep an eye on the concomitant medications specially those which promote weight gain such as antipsychotics, antidepressants, SSRIs, anticonvulsants, MAO inhibitors. Alternative medications should be prescribed to avoid obesity. [9]

Statins are the keystone for lipid management in diabetic patients as they lower both cholesterol and even TG levels to a lesser extent. Ezetimibe is an excellent option for add-on therapy when target is not achieved by maximum dose of the statins. The poor glycemic control should be considered first and improved if possible. The younger patients with type 2 diabetes mellitus will get benefit from statins as it decreases the risk of CVD. [10]

### **Factors affecting Physician in Prescribing Medications**

There are various factors which play a vital role in patient health during diabetes treatment out of which the most important factor is prescribing trends of physician. In our analysis, we found that Physicians are the Primary decision makers in Medical field. Physicians' prescribing decisions are the key for hospitals dominance over the health sector but there are various other Factors also which affect the Physicians decisions like Physicians personal attribute, cost of the medicine and Pharmaceutical resources in the organization which also influence the prescribing decision of physician. [31] Pharmaceutical companies know how important the Physicians are for the health sector and for their own mutual benefits they influence the Physicians and not only Pharmaceutical companies influencing Physicians but Physicians are also get attracted towards their high profile offers. The pharmaceutical companies need to show how different their product is to increase their market share. Pharmaceutical companies usually do face to face detailing, provide medicine samples, provide written evidence, organize meetings, organize medicine launches, sponsor continuous medical education and provide gifts. [32] The type of advertising and promotion strategies is dynamic based on the physicians' reactions. [33] But this is not enough sometimes patient over smartness also affect the treatment the knowledge of the patient on pharmaceutical products which

makes the patient request for a specific medication and alters patient expectations. Generally, Patient's pressure on physicians may lead to unnecessary prescribing and referral. Some studies showed that the involvement of patients in their care selection made physicians to change prescribing decision also.<sup>[34]</sup> And it has been proved that Branded products are always expensive than local products therefore the brand prescription is less affective on prescription behavior of physician because of the cost factor.<sup>[35]</sup> There are many other factors also like treatment factors that commonly influenced the selection of metformin by specialists (93%, 91%, 89%, 87%, and 85%, respectively) and by nonspecialists (80%, 92%, 81%, 86% and 75%, respectively). Considerable scientific evidence (81%) and PPG lowering effect (75%) were other factors that significantly drove the selection of metformin by nonspecialists found that DPP-4 inhibitor have low risk of gastrointestinal side effects, improvement in insulin resistance, effect on glucagon protection of b-cell function, and frequency of administration. When DPP-4 were chosen.<sup>[36]</sup> But in our analysis we have found that if we give metformin as the first line treatment there are less chances of weight gain improvement in insulin resistance, and PPG-lowering effect also. Age also play a major role in this age has certainly proven to be an important factor that will influence the choice of drugs.<sup>[37]</sup> Because many older people live with one or more chronic diseases and often face significant challenges,<sup>[38]</sup> and due to their inoppropiate history they are misdiagonosed and adverse drug reaction appears. <sup>[39]</sup> And last but not the least rest of the factors depends on the physicians experience and qualification a study was conducted in Greece on the "Factors influencing prescribing behaviour of physicians in Greece and Cyprus: results from a questionnaire based survey", which tells that drug clinical effectiveness is the most important factor considered by physicians when they prescribe drugs. However, pharmaceutical form, recommended daily dose, and patient own preferences are taken into consideration more by Greek physicians compared to their Cypriots colleagues. Which proves that Greece doctors are more qualified and experienced. <sup>[40]</sup>

### **Newer Anti-Diabetic Drugs**

With the increasing global pandemic of diabetes especially type 2 diabetes mellitus. Major pharmaceutical companies that are focusing on the newer diabetic agents for the better management of diabetes some of them are SGLT-2 inhibitors, DDP-4, GLP-RAS and

sulfonylurea. SGLT-2 inhibitors and sulfonylureas are frequently used second line drugs because of high efficacy and low costs. By depolarizing the b-cell membrane, sulphonylureas stimulate insulin secretion and, according to a 2010 meta-analysis, thereby lower HbA1c by 1.0–1.25% when used on top of metformin. Their effect on BP and lipids is neutral. Common adverse effects are hypoglycemia and weight gain.<sup>[41]</sup> DPP-4 are also frequently used in the treatment of diabetes .currently there are eight DPP-4 inhibitors in the market namely, alogliptin, anagliptin, gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin and vildagliptin, that are available for the management of T2DM. All these DPP-4 inhibitors have a similar mechanism of action and safety profile. Despite of similar mechanism of action, DPP-4 inhibitors differ in pharmacokinetic and pharmacodynamic parameters, which have great clinical significance practically. Mitsubishi Tanabe Pharma Co. develops Teneligliptin as a novel oral DPP-4 inhibitor which was approved in Japan in September 2012 for the management of T2DM. Currently, teneligliptin is marketed in Japan (Teneria), Argentina, and India presently, teneligliptin is registered in South Korea and is in the pre-registration phase in Indonesia. Additionally, teneligliptin is in phase II clinical trials in Europe, and phase I clinical trials in the US. Teneligliptin, which is classified as peptidomimetic, has a unique structure having five consecutive rings. Due to this unique structure, teneligliptin acts on S2 extensive subsite of DPP-4; this interaction enhances its potency and selectivity.<sup>[42]</sup>

A newer DPP-4 inhibitor for the management of T2DM is Teneligliptin. It provides significant control over blood glucose level within the therapy of 12 weeks, which was further maintained up to 52 weeks with good tolerability. It is useful as monotherapy and in combination with other anti-diabetic drugs. It can be used in T2DM patients with renal impairment and mild-to-moderate hepatic impairment and thus has a unique place in therapy.<sup>[43]</sup> Linagliptin, recently approved by USFDA which is another newer antidiabetic agent under the class of DPP-4 inhibitors.<sup>[44]</sup> Linagliptin are excreted chiefly via the entero-hepatic system and can be used without dose adjustment in patients with renal or hepatic impairment. It has been proved that the efficacy and safety of linagliptin 5 mg once daily for improving glycemic control in adults with T2DM linagliptin in combination with Pioglitazone, did not gain weight or have adverse changes in cardiovascular biomarkers.<sup>[45]</sup>

Now let's talk about the GLP-1 analogs the first marketed GLP-1 analog was Exenatide, which was approved by the FDA in 2005. Exenatide is nowadays used as adjunctive therapy in type 2 diabetes in patients. Currently using metformin, a sulfonylurea, a combination of metformin and sulfonylurea, or a combination of metformin and a thiazolidinedione; they are many other GLP-1 ANALOGS which are under the phase 3 trial. That are also called as EXENATIDE-LAR. Exenatide administered subcutaneously twice daily. Most of the other products in development are administered subcutaneously once daily. [46]

There are many others PPAR- $\gamma$  agonists and SGLT2 inhibitors are still early in phase 3 development. [47] According to our understanding of diabetes, we concluded that diabetes is constantly evolving and GLP-1 RAs represent an important facet of this understanding. [48] But non-pharmacological treatments play also a major role in the treatment of diabetes which includes lifestyle modifications and weight loss. [49] It is noted that physicians till now recommend metformin as the first choice of drug in the treatment of diabetes. [50]

### **Common ADR's of Anti Diabetics**

Adverse drug reactions are the drug related problem which is the most important drawback of drug safety. Every drug has its own ADR so that's why detection of Adverse Drug Reactions (ADRs) has become significant because of introduction of large number of drugs in the last two decades. Adverse drug reactions may occur daily in hospitals and adversely affecting patient's life, most often causing considerable morbidity and mortality. So that's why Attention should be given in identifying the patient populations which are in danger, the drugs most commonly responsible and the causes of ADRs. [51] Increased supply of drugs in the market and an upward trend in polypharmacy are most important contributing factors for the prevalence of ADRs worldwide. Adverse drug reactions can result in loose of patient's confidence leading to negative emotions toward their physician's treatment and can engage in self-treatment options, which may consequently precipitate additional ADRs. [52] WHO has seriously considered this matter by establishing an international adverse drug reactions monitoring centre at Uppsala, Sweden, which is collaborating with national monitoring centers in around 70 countries. The first ADR monitoring programmed started with 12 regional centers and India joined the WHO monitoring program Uppsala, Sweden in 1997

and three centers were started in medical colleges at New Delhi, Mumbai and Aligarh. [53] If we talk about diabetes drug dyspepsia and diarrhea were the most common adverse effect reported by patient to doctors, mostly due to metformin, followed by voglibose. Glimepiride alone or its combination with metformin caused a few incidence of hypoglycemia; all of them have occurred if Glimepiride was used with dose of 2 mg/day or more. [54]

Metformin-induced dyspepsia occurred only if it was used in dose more than 1000 mg/day. Incidence of dyspepsia was also common with use of voglibose, as expected from its mechanism of action. Metformin with voglibose combination produced more frequent incidents of dyspepsia. [55] Interactions with oral hypoglycemic agents are important because the outcomes, particularly hypoglycaemia, are serious. As with all interactions the times of high risk are when a second drug is started, stopped or altered its dose. Regular co-prescription of the same dose of another drug is not likely to cause major problems. [56] ADRs due to OAD are a very frequent problem. Although they are not likely to be life-threatening, but they can cause various types of discomforts in many patients. Few large multicentre studies on this matter need to be done to build a strong ant diabetic drug ADR database. Uncommon side effects, although rare can become bothersome for patients and may lead to decreased medication adherence and hence treatment failure. [57] Careful consideration of the ADRs of anti-diabetics while prescribing, carrying out adequate clinical and laboratory monitoring and proper counseling of patients might help in prevention and early detection of these rare but severe side effects of anti-diabetics.[58] Adverse drug reaction also depends on the Socio-demographic characteristics, Clinical characteristics also which include. These include sex, age, marital status, religion, place of residence, educational status, employment status, smoking status, alcohol consumption and physical activity. Chemical characteristics include BMI, hospitalization, average FBG, presence of co-morbid conditions, number of comorbidities per patient, presence of diabetes complications and number of complications per patient.[59] For this purpose Pharmacovigilance of drug is done by the clinical Pharmacist and doctors. ADR centers have been made in the hospitals for continuous monitoring of the drugs so that each and every drug reaction has been noted and send to the government. And best quality of treatment should be provided to them. [60]

## **Tackling Diabetes Mellitus & COVID-19**

An editorial by Akhil Shenoy et al. studied the association of diabetes and COVID-19. The COVID-19 patients are having diabetes as one of the most common co-morbidities which was found to be 7% of the total COVID patients. In USA, approximately one third of the patients admitted in the ICU were having diabetes as an underlying health condition. A study in China demonstrated that when diabetic and non-diabetic patients with severe covid-19 were compared, it was found that diabetic patients were having severe inflammatory response. They were more probable to receive ventilation and reduced duration of survival (higher mortality). The survival of patients with diabetes on hospitalization was independent of glycaemic control. [61]

Another study by Sten Madsbad et al stated that in December 2019, patients with pneumonia like symptoms emerged out in Wuhan (China) caused by novel coronavirus. A transgenic mouse was used to study the association between the DPP-4 receptors and pulmonary alveolar cells to know the effect of diabetes in worsening the disease. It was found that patients with diabetes have greater weight loss and greater pulmonary inflammation due to macrophage infiltrates as seen in COVID-19. [62]

In COVID-19 infection, diabetes is a risk-factor for patient's hospitalization and mortality. In a study of 52 ICU patients, 32 were non-survivors out of which 22% of patients were having diabetes as co-existing illness. While comparing the ICU and non-ICU patients of coronavirus disease, there is an increase of two times in the patients of ICU whereas mortality is 3 times more in people with diabetes than non-diabetic COVID patients. Poor glycaemic control makes the patient more prone for serious infections whereas risk of infections increases due to poor glycaemic control. The problem is that the treatment of hyperglycemia is tough during infections and the infection can lead to loss of glycaemic control. More frequent blood glucose monitoring and continuous change in anti-diabetic treatment are done to control blood sugar level. The patients with type 2 diabetes mellitus and with moderate to severe illness, metformin and SGLT- 2 inhibitors should be stopped. Sulphonylureas may lead to hypoglycaemia. DPP-4 inhibitors and linagliptin can be used in renal compromised patients without risk of hypoglycaemia. [63]

The level of D-dimer and FIB was remarkably higher in diabetic patients which indicate that they are more prone to a hypercoagulable state. The insulin demand in diabetic patients

increased after the infection of SARS CoV-2 as it alters glucose metabolism. This will lead to poor glycemic control and will further amplify the severity of pneumonia. It proves that diabetes is a risk factor for prognosis is more severe as compared to non-diabetic patients by examining organ damage, inflammatory factors or hypercoagulability. [64]

Covid-19 has spread from China very rapidly and has shown a broad spectrum of severity. In vitro studies have indicated that hyperglycemia enhances the replication of viral genome as the pulmonary cells are exposed to high concentration of glucose; it increases the influenza virus infection. Early isolation, diagnosis and management can lead to better control over this pandemic. The co-morbidities like diabetes are remarkable predictors of mortality and morbidity in COVID-19 patients. Infection of COVID-19 in diabetic patients triggers the high stress conditions which promotes the release of hyperglycemic hormones eg. Glucocorticoids and catecholamines, which leads to increased blood sugar levels. In a Chinese study, 39 covid patients without diabetes, who didn't received steroid therapy were compared with 39 healthy volunteers. It was found that 20 out of 39 covid patients developed diabetes during their hospitalization period. It is supposed that coronavirus have damaged the islets of pancreas which is evident from immune-staining in which it was found that ACE2 were strongly present there. [65]

The more vulnerable people for COVID-19 infection are the elderly and those having pre-existing medical condition. COVID-19 as other respiratory infections spreads via air droplets. The virus can survive from few hours to few days. Social distancing along with hand hygiene should be maintained. Avoid close contact with the infected person. [66]

The clinical manifestation on the patient can range from mild to severe disease which requires admission in ICU and ventilator support. Based on an observational study on clinical benefits in patients of coronavirus disease, ICMR has suggested a combination therapy of Lopinavir and Ritonavir. It is difficult to initiate this treatment until the patient gets symptoms of severe illness. The patients of high risk group associated with high risk of mortality should initiate this combination therapy. The limitation of this treatment is that it is approved for emergency public health use. [67]

There are certain measures that should be taken in diabetic patients. Notify to the health authority if fever, cough, running nose or dyspnoea is observed in the patients. The affected

person should be isolated for 14 days till the symptoms resolves. Oral agents like metformin and SGLT-2 inhibitors need to be stopped. Insulin is preferred to treat hyperglycemia. Frequent monitoring of blood glucose level is done. Hydration should be maintained and steam inhalation should be done for symptomatic treatment. [68]

The insulin dose may need adjustment specifically the basal insulin dose when insulin sensitivity is altered example improving infection, recovering COVID-19 and decreased corticosteroid therapy. [69]

There is an abnormal inflammatory state in diabetic patients. They are highly susceptible for infections. Hyperglycemia influences the incidence and course of sepsis. Insulin therapy decreases inflammation and is helpful in glycemic control. Hypoglycemia is dangerous to critically ill patients. [70]

## CONCLUSION

By and large, the one and best way to manage diabetic patients and avert them from complications is to maintain glycemic control. The fluctuating blood glucose level results in compromise with their quality of life. The prescriber's priority must be to provide best, effective and pocket friendly treatment to the patients. Besides, hypertension is the most prevalent comorbidity in diabetic patients followed by hyperlipidemia, cardiovascular disease, obesity and kidney disease. The physician's choice of anti-diabetic drug depends upon various factors which include FBS level, HbA1C level, insulin resistance, renal impairment and other patient related factors. Nowadays, there are various newer anti-diabetic agents which are highly effective in maintaining blood glucose level. Linagliptin has emerged out as a boon for diabetic patients with renal and hepatic impairment as it does not require dose adjustment. Teneligliptin has good glycemic control and can be prescribed to renal and mild-moderate hepatic impairment. The diabetic patients should be monitored for ADRs as the therapy for diabetes runs for a longer duration. Diabetic patients are more prone for mortality by COVID-19 infection and it worsens the disease. Maintaining blood glucose level can decrease the mortality in diabetic patients hence, continuous monitoring should be done. Eventually, we would like to conclude that diabetes is not life-threatening until or unless the blood glucose level is disturbed.

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