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Review Article

A short review on impact of Covid-19 in diabetic chronic kidney disease patients

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ABSTRACT

Patients with diabetes and chronic kidney disease including end-stage kidney disease, and kidney transplant recipients are at increased risk of severe COVID-19 infection, hospitalization and premature death. Both diabetes and CKD exert synergistic effect on increasing the patient's susceptibility towards risk of COVID-19 infection. The Global Burden of Disease collaboration (GBD) and WHO have declared CKD and diabetes as the most prevalent risk factors for severe COVID-19. Hence, management should focus on both infection prevention and treatment. Several studies and adequate evidence from literature is available on the impact of COVID-19 disease on diabetes alone or CKD alone. However, many data is not available on COVID-19 disease impact on diabetic CKD patients. This short review article focuses on understanding the impact of COVID-19 on diabetic CKD patients and other aspects such as pathophysiology, epidemiology, prevention and management of diabetic CKD patients with COVID-19 infection.

1. Introduction

COVID-19 pandemic caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is believed to be representing a real challenge to the health care stream due to its economic impact on surge in health system's capacities and on patient health. Interestingly, this novel COVID-19 disease is known to exert adverse effects with higher rates of complications mainly on elderly patients and patients with co-morbidities such as diabetes, hypertension cardiovascular disease, renal, or hepatic impairment etc. COVID-19 predisposes the patients to 3-4-fold increase in the risk of developing acute respiratory distress syndrome (ARDS) resulting in respiratory failure, intubation, COVID-19 pneumonia, Intensive Care Unit (ICU) admission or even death among patients with existing co-morbidities. Although it is commonly known that COVID-19 infection mainly causes respiratory illness with highly varying clinical manifestations, evidence gathered over time shows that it also affects other organs with the kidney being one of the main site of complications.

Chronic Kidney Disease (CKD) is defined as a decline in the functioning of kidneys measured by glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2, >30 mg/g of urinary creatinine or evidence of kidney damage (even with normal GFR), such as increased albuminuria ≥200 μg/min, abnormal urine sediment or structural abnormalities persisting for >3 months, with implications for health. It is one of the major causes of all-cause morbidity and mortality among diabetic patients. It is estimated that about 30–40% of diabetic patients develop CKD. Diabetic patients are easily prone to infections due to immune dysfunctions. This becomes more worse in case of diabetic patients with CKD as they express a chronic systemic inflammation that adds to the immunosuppressed state that accounts for most of the chronic complications including kidney failure, Acute kidney Injury (AKI) and premature death from many causes, including, but not limited to, cardiovascular disease and

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bacterial and viral infections.[1,2]

Diabetic patients with severe CKD (Stage 4 and 5), requiring dialysis and kidney transplant are at higher risk of COVID-19 infection, poor outcomes, and often present atypical clinical features that constitute an additional challenge. Several studies and adequate evidence from literature is available on the impact of COVID-19 disease on diabetes alone or CKD alone. The Global Burden of Disease collaboration (GBD) and WHO have declared CKD and diabetes as the most prevalent risk factors for severe COVID-19. However, much data is not available on COVID-19 disease impact on diabetic CKD patients.[3]

2. Pathogenesis and Epidemiology

Evidence shows that the mechanism of SARS-CoV-2 virus is similar to that of the previous coronavirus SARS-CoV which includes binding of the virus to the host target cells via angiotensin-converting enzyme 2 (ACE2). The diabetic CKD patients often have a substantially increased expression of ACE2 as they are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs), which put them at high risk of infection with SARS-CoV-2 virus.[4]

In a study of anonymized patients records of symptomatic COVID-19 patients (2092 patients with

CKD only and 742 patients with diabetic nephropathy) from Mexican Open Registry of COVID-19 patients performed by Leon-Abarca JA et al to analyze the prevalence rates of COVID-19 infection, development of COVID-19 pneumonia, admission, intubation, ICU admission and mortality; the adjusted prevalence analysis revealed that there was an 87.9% higher probability of developing COVID-19 pneumonia in patients with diabetic nephropathy, a 5% higher probability of being admitted, a 101.7% higher probability of intubation and a 20.8% higher probability of a fatal outcome due to COVID-19 pneumonia in comparison to CKD patients ($p<0.01$). The study concluded that both CKD and diabetic nephropathy disease conditions showed similar higher rates of COVID-19 pneumonia, intubation and case-fatality compared to overall population. While patients with diabetic nephropathy had nearly a 2-fold higher rate of COVID-19 pneumonia, intubation, ICU admission, and death compared to patients with CKD alone.[4]

In another recently published OpenSAFELY study done by Williamson EJ et al, data obtained and analyzed from 17 million patients showed that dialysis (adjusted hazard ratio (aHR) = 3.69), organ transplant (aHR = 3.53) and stage of CKD (aHR = 2.52 for patients with eGFR <30 mL/min/1.73 m2) were the three major co-morbidities associated with highest rate of mortality among COVID-19 patients with diabetic CKD. The risk associated with low eGFR was higher than the risk associated with diabetes (aHR range 1.31–1.95, depending upon the level of glycemic control) or chronic heart disease (aHR = 1.17).[5]

3. Risk Factors of Covid-19 among Diabetic CKD Patients

Diabetes and CKD individually or in combined form they themselves serve as the major risk factors for COVID-19 infection. Other traditional, non-traditional and dialysis related risk factors for diabetes and CKD also serve as the primary risk factors for COVID-19 infection as well.

3.1. Precautions and Management of Covid-19 Among Diabetic CKD Patients

General precautions that need to be taken to prevent COVID-19 infection among diabetic CKD patients include:

There is no specific treatment protocol or guideline for management of COVID-19 infection among diabetic CKD patients. Therefore, treatment should be based on individual patient needs aiming at both prevention and management of infection. Good glycemic control by use of oral hypoglycemic drugs, insulin etc. Use of steroids, antiviral drugs and symptomatic treatment are advisable.

Government of India Ministry of Health & Family Welfare has issued a Diagnosis and Management of Diabetes at COVID-19 Patient Management facility on June 1, 2021.[6]

Patients requiring regular dialysis due to maintenance dialysis, AKI and Continuous Renal Replacement Therapy (CRRT) should adhere to prescribed schedule and not miss their dialysis sessions to avoid any emergency dialysis. Patients on peritoneal dialysis should maintain at least 2 weeks of peritoneal dialysis supplies with real-time monitoring of vital signs and treatment data. Home visits by healthcare workers should be avoided except for patients with disabilities or in case of an emergency. Patients with end-stage kidney disease on in-center hemodialysis should be screened for COVID-19 symptoms and temperature checks for patients and staff depending on institution policy.[7]

No adequate evidence and/or treatment protocol or guideline recommendations are available optimal management of COVID-19 infection in Kidney transplant recipients (KTRs), the population that has high susceptibility to infections due to immunocompromised state. In ambulatory recipients with COVID-19, the immunosuppression regimen is continued without any changes. For inpatient recipients with mild COVID-19 and no supplemental oxygen requirements, reducing the dose of mycophenolate mofetil while maintaining the rest of the immunosuppression regimen including steroid therapy is recommended. While in those with severe COVID-19 infection requiring supplemental oxygen, dexamethasone or remdesivir, or both, it is recommended to discontinue mycophenolate mofetil while continuing the calcineurin inhibitors but targeting a lower trough level (eg. Tacrolimus

Table 1: Risk factors of COVID-19 among diabetic CKD patients.

Traditional Risk Factors	Non-traditional Risk Factors	Dialysis Related Risk Factors
• Uncontrolled diabetes and its complications • Hypertension • Dyslipidemia • Elderly age • Smoking • Metabolic Syndrome (MetS) • Overweight or Obesity • Hyperhomocysteinaemia	• CKD and/or renal failure • AKI • Calcium, phosphorus and electrolytes imbalance • Chronic inflammation • Renal transplant (graft failure, use of immunosuppressive therapy after transplant) • Other chronic renal disease complications including low eGFR, increased albuminuria, serum creatinine, retention of uremic toxins, elevated levels of certain cytokines and increased inflammatory-poor nutrition" state.	• Dialytic changes (both inter- and intra-) • Bio-incompatibility of membranes • Dialysate impurity

Table 2: Guidance diagnosis and management of diabetes at.

1.	Social distancing and personal hygiene – highly recommended
2.	Healthy and balanced diet and exercise as suggested by the nutritionist or health care provider
3.	Use of Personal Protective Equipment (PPE) as recommended by the CDC
4.	Education of health care workers and patients on advances in COVID-19
5.	Good glycemic control – regular blood glucose monitoring
6.	Continue regular medication and regular health check-ups with health care provider
7.	Regular ketone level monitoring especially among those with persistent hyperglycemia
8.	Periodic renal functioning tests
9.	Minimize or avoid smoking and alcohol
10.	Stress management
11.	Minimize exposure to COVID-19 by adapting virtual visits via telemedicine/home drug delivery
12.	Follow vaccination schedule

trough level 4–6 ng/mL). RAS inhibitors should be continued in those with stable CKD. Remdesivir should be avoided in patients with GFR <30 mL/min/m^2unless the benefits outweigh the risks. [8]

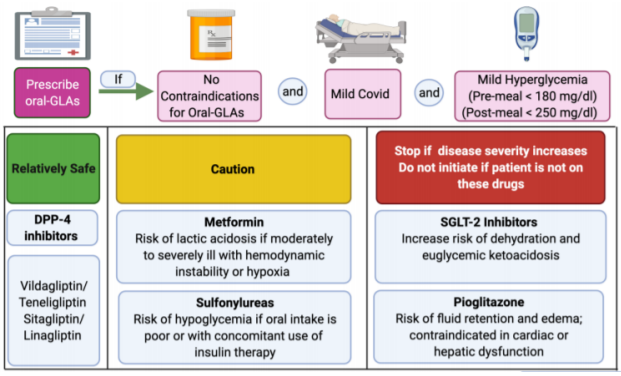

Fig. 1: Guidance on the use of oral glucose lowering drugs (Oral-GLAs) among COVID-19 patients. [Adapted from reference 6: GoI, MHFW guidance diagnosis and management of diabetes at COVID-19 patient management facility, 2021.]

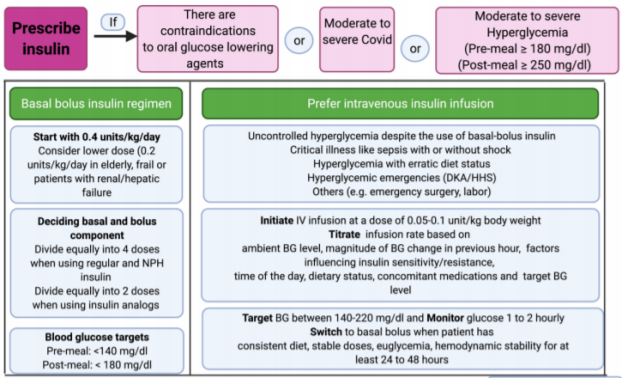

Fig. 2: Guidance on the use of insulin therapy among COVID-19 patients. [Adapted from reference 6: GoI, MHFW guidance diagnosis and management of diabetes at COVID-19 patient management facility, 2021.]

4. Discussion and Conclusion

Diabetes and CKD are common diseases that show synergistic association with premature mortality, decrease in both length and quality of life. Diabetic patients with or without CKD often have a significantly reduced forced vital capacity and forced expiratory volume of the lungs and other pathophysiological conditions such as proinflammatory state and reduced innate and adaptive immune systems. These conditions could also predispose these with COVID-19 to have a worse prognosis. Furthermore, immune-modulating therapies used to treat these conditions can also add to the immune dysregulation

making the patients susceptible for increased risk of infections. It has been reported that increased levels of HbA1c is associated with an increase of 60% in risk of hospitalization and severity of pneumonia in bacterial infections among diabetic CKD patients. Poor glucose control in many diabetics could promote glycosylation of ACE2, the susceptible cell for COVID-19 virus in the host.

Several other plausible explanations can be given for an increased incidence and severity of COVID-19 infection among diabetic CKD patients which include poorly controlled diabetes that promotes glycosylation of ACE2 leading to overexpression of ACE2 receptors, the susceptible cells for COVID-19 virus; hyperglycemia or increased HbA1c that are associated with increase in 60R risk of hospitalization and severe bacterial infections such as pneumonia, and need for routine dialysis which implicated the patients to pay frequent visits to the hospital or healthcare facilities there by paving a way for direct or indirect contact with infected patients, contracting the infection etc.

Several studies and adequate evidence from literature is available on the impact of COVID-19 disease on diabetes alone or CKD alone. However, much data is not available on COVID-19 disease impact on diabetic CKD patients as limited number of studies have assessed the clinical picture of COVID-19 in patients with diabetic CKD, conducted in a few countries only. Based on the fact that both diabetes and CKD individually or in combined form serve as the major risk factors for COVID-19 disease, there is a dire need to study the severity of the COVID-19 disease course in diabetic CKD patients. Thus, further research is warranted in various settings on several aspects of this topic such as detailed epidemiological information that could allow the probability analysis on different clinical outcomes based on the staging of the renal disease, glycemic control etc., that could affect the patient's course of the disease and could help fill the knowledge gaps and help formulate clinical care guidelines for management of these patients.

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7. Conflict of Interest

The author declares that there is no conflict of interest.

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