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Review

A Review of the Interrelationship Between COVID-19 and Diabetes Mellitus

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Article information

Received date: 22/05/2020; **Accepted date:** 25/06/2020; **Published date:** 30/06/2020

Abstract

In this pandemic of coronavirus disease 2019 (COVID-19) the presence of diabetes mellitus has evolved as a key factor determining the outcome of patients. Various hypotheses have been put forward to explain the relationship between the two. Treatment options of type 2 diabetes mellitus (T2DM) may need to be reconsidered and various factors kept in mind while determining the drug of choice in the presence of COVID-19. Conversely, the presence of diabetes mellitus as a comorbid factor may affect the prognosis of patients of COVID-19.

Keywords: Diabetes mellitus, COVID-19, morbidity, hyper coagulation

Introduction

COVID-19 is a major health care crisis that has taken the world by storm. This infection which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has its origin traced to Wuhan, China. Various studies have established diabetes mellitus (DM) as a frequent co-morbidity as well as an independent prognostic factor in COVID-19 patients.

Impact of Diabetes in SARS-CoV-2 Infection

In a study of around 1100 COVID-19 patients, 7.4% had diabetes which increased to 16.2% among patients with severe disease and around 27% among patients of ICU admission, mechanical ventilation and death.[1] A meta-analysis of 12 studies of COVID-19 in patients with diabetes concluded that though diabetes does not increase the risk of SARS-CoV-2 infection it is associated with worse outcome of the disease.[2] The pooled rate ratio of diabetes in SARS-CoV-2 infection was 2.26 calculated among patients with adverse disease as compared to the ones with more favourable courses.[2] Another meta-analysis of 33 studies found a pooled odds ratio of 2.16 in terms of severity and mortality in diabetics.[3] An epidemiological study found a mortality rate of 7.3% in patients of COVID-19 with diabetes as compared to 0.9% in that of patients without any comorbidities.[4] Fasting plasma glucose had earlier been found to be independently associated with an increased hazard ratio of mortality with SARS infection.[5]

What Could be the Cause of Increased Complications and Mortality in Type 2 Diabetes Mellitus ?

It is a well-accepted fact that infections are more common in patients with diabetes mellitus because of alterations in their immunity. Both humoral and cellular innate immunity have been found to be dysfunctional at various levels among diabetics which is more marked in those with poor glycaemic control.[6] The combination of coronavirus infection and T2DM triggers an altered dysregulated immune response which can lead to an aggravation in the condition.[7] Patients with T2DM are in a state of metabolic inflammation which also predisposes them to an increased release of cytokines.[8] Cytokine storm has been implicated in multi-organ failure in patients with severe SARS-CoV-2 infection. The expression of angiotensin-converting enzyme 2 (ACE2) which has been identified as a receptor for SARS-CoV-2 is markedly increased in patients with diabetes mellitus.[9] Diabetes mellitus also has been demonstrated to induce expression of the angiotensin-converting enzyme in the lung, liver and heart which may be an explanation for the increased incidence of multi-organ failure in diabetic patients with SARS-CoV-2 infections.[10] A direct role of corona virus in causing acute diabetes by binding to ACE2 receptors located in the islet cells of the pancreas has also been proposed.[11] The presence of obesity in a large proportion of type 2 diabetic patients

and its association with inflammation, impaired immunity, oxidative stress and mechanical restriction of ventilation has also been postulated to be an important determinant of prognosis of COVID-19.[12,13]

Impact of SARS-CoV-2 Infection in Diabetes

Infection with SARS-CoV-2 has been found to have an adverse impact on the patient's glucose metabolism in clinical studies which can lead to a vicious cycle of events. In a study of 658 hospitalized COVID-19 patients, 6.4% were found to present with ketosis, of which a large proportion were diabetics in whom the chance of progressing to ketoacidosis was high.[14]

Treatment of Diabetes in COVID-19 Patients

A number of bodies including the American Diabetes Association (ADA), International Diabetes Federation (IDF) and Research Society for the Study of Diabetes in India (RSSDI) have also brought out guidelines for the preventive management of COVID-19 among diabetics which are not grossly different from those advocated for the nondiabetic population .They advocate the importance of hygiene and physical distancing while emphasizing on the importance of good glycaemic control. The American Diabetes Association has formulated some general recommendations for patients with COVID-19 having diabetes: avoidance of dehydration, maintenance of glycaemic balance close to the individualized target values, monitoring of blood sugar levels to avoid hypoglycaemic episodes as also to prevent ketoacidosis and adherence to strict hygiene measures.

In keeping with the understanding of the association between diabetes and SARS-CoV-2 and its implication on the prognosis of patients, strict glycaemic control of patients has been advocated. The choice of medications to treat diabetes in the context of corona virus infection would depend on the severity of the disease. While in severe infection insulin would be the obvious choice, in the setting of mild to moderate infection without complications, oral hypoglycaemic agents may be used. In the context of COVID-19 apart from their role in glycaemic control there are other factors involved which could play a role in determining the choice of the oral hypoglycaemic drug to be used.

A. DPP4 inhibitors and COVID-19

Structural studies have predicted an interaction between SARS-CoV-2 spike glycoproteins and dipeptidyl-peptidase 4 (DPP4) glycoprotein. However, that still awaits confirmation in human cells.[15] The enzymatic activity of DPP4 has been found to affect the function of several cytokines, chemokines and growth factors and thereby have a potential to increase inflammation.[16] The higher plasma DPP4 levels in diabetes, obesity, metabolic syndrome and elderly individuals as also the broad distribution of DPP4, could probably explain the increased involvement of multiple organs and the increased mortality and morbidity associated with these conditions.[17] Measurement of plasma DPP4 levels as a tool for risk stratification and as a marker of disease progression and response to treatment in diabetic patients infected with SARS-CoV-2 has also been advocated.[18] With these potential associations in mind, the role of DPP4 inhibitors in preventing the binding of SARS-CoV-2 and thereby decreasing the risk and severity of acute respiratory complications has been considered.[16] However, in Middle East Middle East Respiratory Syndrome (MERS) where a much stronger association of DPP4 with viral binding has been established, no benefit was seen with DPP4 inhibitors.[19] Clinical trials are underway with DPP4 inhibitors in mild to moderate COVID-19 patients with diabetes and definite data is yet to be published .

B. SGLT2 inhibitors and COVID-19

With the potential risk of dehydration and diabetic ketoacidosis in mind stopping the sodium-glucose co-transporter-2 (SGLT2) inhibitor group of drugs in the stage of acute infection is generally advocated.[20] In those with mild disease in whom the glycaemic control is adequate and the health care professional is not keen to change the SGLT2 inhibitor in use, regular monitoring of the renal function and clinical state is to be maintained. Promotion of renal ACE2 activity by SGLT2 inhibitors has also been demonstrated which could have a role in prognosis.[21] However interestingly a hypothesis has been put forward that by preventing the lowering of cytosolic pH and thereby reducing the viral load dapagliflozin can prevent the severe course of COVID-19 infection.[22] Also based on the data on the positive effect of dapagliflozin on heart failure, a randomized phase 3 trial- Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE 19) has been initiated in patients of COVID-19 with a medical history of hypertension, T2DM, atherosclerotic cardiovascular diseases (CVD), heart failure with

reduced or preserved ejection fraction or chronic kidney disease (CKD) stage III to IV to evaluate the role of the drug in the progress, clinical complications and death .

C. Metformin and COVID-19

Metformin has been demonstrated to exert anti-inflammatory actions in preclinical studies and reduce circulating biomarkers of inflammation in people with T2DM. Metformin use has been found to reverse lipopolysaccharide-induced pulmonary oedema, vascular leakage, neutrophil accumulation and attenuate lipopolysaccharide (LPS) induced production of tumour necrosis factor-α (TNF-α) and interleukin 6 (IL-6) and also to reduce TNF-α-induced activation of the nuclear factor kappa B (NF-κB) axis.[23] The anti-inflammatory actions of metformin have been found to be independent of glucose levels. On the other hand, reports studying antibody titres in a small number of individuals have suggested that immune responses to influenza vaccination are modestly impaired in metformin-treated subjects.[24] The clinical significance of these in terms of use of metformin in COVID-19 patients presently remains uncertain.

Dehydration and risk of lactic acidosis (particularly in the setting of hypoxia in severe COVID-19 infection) remain areas of concern and may thereby necessitate temporary stopping of metformin in severe infection or conditions of dehydration.

D. Pioglitazone and COVID-19

Pioglitazone use has been associated with upregulation of ACE2 in insulin-sensitive tissues in rats and reduction of a disintegrin and metalloproteinase domain 17 (ADAM-17) which cleaves ACE2 and inactivates it in human skeletal muscles and therefore, theoretically speculated to present a risk of poor outcome.[25,26] Conversely, the anti-inflammatory roles of pioglitazone in diabetic patients has also been seen in multiple studies and could also represent a potential beneficial effect.[27,28]

E. GLP-1R agonists and COVID-19

Glucagon-like peptide-1 receptor (GLP-1R) agonists have been demonstrated to exert broad anti-inflammatory actions in animals with experimental inflammation and reduce biomarkers of systemic inflammation in human subjects with type 2 diabetes and in people with obesity. Multiple preclinical studies demonstrate that GLP-1R agonists attenuate pulmonary inflammation, reduce cytokine production and preserve lung function in mice and rats with experimental lung injury.[29,30] GLP-1 has been found to be safe in short term studies of ventilated patients with critical illness.[31] However, the effect of the action that liraglutide has on the activity of the angiotensin-converting enzyme 2/angiotensin-(1–7)/mitochondrial assembly receptor [ACE-2/Ang (1-7)/Mas] receptor pathway and its consequence in COVID-19 remains an area of concern.[32] GLP-1RA therapy should be discontinued in patients with haemodynamic instability, renal dysfunction and gastrointestinal dysfunction. There is insufficient experience with the safety and use of GLP-1R agonists in critically ill subjects to make therapeutic recommendations for use of these agents in the context of coronavirus infection.

F. Sulphonylurea and COVID-19

Caution with the use of sulfonylureas in terms of the risk of hypoglycaemia needs to be exercised particularly if chloroquine is used in the treatment protocol of SARS-CoV-2.

G. Hydroxychloroquine and COVID-19

Hydroxychloroquine has in recent years attracted interest as a potential therapeutic intervention for patients with T2DM. Potential pathways of action of hydroxychloroquine in COVID-19 infection include alteration of endosomal pH, interference with glycosylation of cellular receptors and increase in the influx of zinc ion, all of which facilitate the entry and subsequent action of the virus into the cells.[33]

Till mid-April, 142 trials had been registered involving chloroquine and hydroxychloroquine either alone or in combination in the prevention or treatment of COVID-19. While a few studies have demonstrated a positive role of hydroxychloroquine many others have failed to reciprocate such results.[34-36] Hydroxychloroquine has been known to cause QT interval prolongation and life threatening arrythmia. Keeping this in mind till the time of writing of this article, the FDA had issued a caution against the use of hydroxychloroquine for COVID-19 outside of a hospital setting or a clinical trial.

H. Insulin and COVID-19

Insulin remains the mainstay of treatment of any moderate to severe infections and that is not any different with SARS-CoV-2. A study has reported that patients with hyperglycaemia who are treated with insulin infusions have a lower risk of severe disease.[37] Insulin doses might need to be titrated based on frequent glucose and ketone monitoring to avoid both hyperglycaemia and hypoglycaemia and correctional bolus of insulin might be needed to be added to avoid severe hyperglycaemia and ketoacidosis. In a retrospective study, existing insulin use was associated with an increase in death linked to COVID-19. Though it was not clear whether the cause of this was insulin itself or the patient characteristics, the authors concluded that more attention was needed in this group of patients.[38]

I. Statins and COVID-19

Statins also cause upregulation of ACE2. However, keeping in view the risk of rise in lipids and the potential cardiovascular risk ,the risk of rebound rise in inflammatory markers like IL-6 and interleukin-1β (IL-1ß) as also the long-term benefits associated with statins it is advocated to continue the use of statins.[39] However, when lopinavir/ritonavir or remdesivir are used for the treatment of COVID-19 concurrently with statins, there are concerns of increase in serum levels of statins and consequent myopathy and hepatotoxicity.[40]

J. ACE inhibitors and COVID-19

It has been well established that 2019-nCoV uses the receptor angiotensin converting enzyme 2 (ACE2) for its entry into the host cells.[41] ACE inhibitors and angiotensin receptor blockers (ARBs) upregulate ACE2 expression and have thus been postulated to facilitate infection with SARS-CoV-2.[42] ACE2 gene polymorphism has been linked to an increased risk of diabetes and thereby may also predict susceptibility to SARS-CoV-2. These data have triggered concern about the use of RAAS inhibitors and the probable increase in the risk of infection and development of complications in this COVID-19 pandemic. On the other hand, low angiotensin II levels due to angiotensin-converting enzyme 1 (ACE1) inhibition may mitigate the anti-inflammatory effects mounted by angiotensin 1-7. A number of cohort studies have not found an association with increased risk of COVID-19 with current use of renin-angiotensin-aldosterone system (RAAS) inhibitors.[43] Present evidence is still inadequate to comment regarding the direction of tilt of the risk benefit ratio with the use of ACE1 or angiotensin receptor blockers amongst diabetics with COVID-19 infection.[44] A joint statement from the American College of Cardiology (ACC), American Heart Association (AHA) and Heart Failure Society of America (HFSA) has advocated against stopping these groups of medicines in those who are already on them till more data is available.

Treatment of Covid-19 in Patients with Diabetes

While the treatment of patients with COVID-19 is being done in accordance with different protocols, in patients with diabetes certain aspects need to be considered.

A. Hypercoagulability in COVID-19

COVID-19 patients with diabetes have been found to be at a hypercoagulable state with higher risk of uncontrolled inflammatory responses. Diabetes per se is a hyper coagulable state .The constellation of coagulation abnormalities associated with diabetes include enhanced activation of platelets and clotting factors, elevation of levels of fibrinogen, factor VII, factor VIII, factor XI, factor XII, kallikrein, von Willebrand factor, prothrombin activation fragment 1+2, thrombin–anti-thrombin complexes, increase in circulating platelet aggregates, decrease in the levels of the anticoagulant protein C, increase in plasminogen activator inhibitor type 1 (PAI-1), increase in platelet aggregation in response to platelet agonists, increased platelet contractile force (PCF) and presence of higher plasma levels of platelet release products such as β-thromboglobulin, platelet factor 4 and thromboxane B2.[45] Micro and macro-circulatory thrombosis has been found to be a major mechanism for multi organ dysfunction in COVID-19.[46] Retrospective analysis of COVID-19 patients have demonstrated altered coagulation profile including reduced activated partial thromboplastin time (APTT), extended APTT and an extended PT.[47] D dimer levels which been shown to be significantly higher in those with diabetes compared to non-diabetics, have also been found to be good

predictors of in hospital mortality in COVID-19.[48] The association of the hyper coagulable state prevalent in diabetes could have a role to play in the associated increase in morbidity and mortality.

B. Corticosteroids and COVID-19

There is no consensus regarding the use of corticosteroids in the treatment of COVID-19. While some studies have given positive results others have not found any benefit with the use of corticosteroids.[49,50] The World Health Organisation (WHO) guidance on clinical management of SARS-CoV-2 infection advises against the use of corticosteroids except for in clinical trials. When used in diabetics the impact of these drugs on the glycaemic levels and immune response should be taken into consideration.

Apart from these, some other specific concerns in diabetes include interference with the accuracy of certain CGM sensors in patients given paracetamol, risk of hyperglycaemia and altered lipid profile with lopinavir/ritonavir and hypoglycaemia with chloroquine.[51,52]

Conclusion

In this pandemic of SARS-CoV-2 infection, diabetes has emerged as one of the major predictors of mortality and morbidity. Various aspects of the pathophysiology and treatment of diabetes mellitus and COVID-19 have been found to have mutually significant consequences but many areas still remain in the grey zone and need to be understood better. Future research is needed to reach a state of better understanding of the interrelationship amongst the two.

Declaration of conflicting interests

The author declares no conflict of interest.

Funding

No funds were received for the study and publishing this article.

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