Editorial

Covid-19 and Diabetes Mellitus

Diabetes and infections have a bidirectional relationship. Hyperglycaemia increases the risk of acquiring infection and the propensity to develop more severe disease and its attendant adverse outcomes. On the other side, the infection may result in new-onset (stress hyperglycaemia) or worsening of pre-existing hyperglycaemia through many inflammatory mediators and stress hormones. An example pertinent for India is tuberculosis (TB), which can lead to new-onset diabetes.[1] Conversely, diabetes can increase the chances of treatment failure and death in individuals with TB.[2] Allard *et al*. found that diabetes significantly increases the risk for hospitalization after infection with the 2009 H1N1 virus.[3]

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is a recent viral infection that originated from Wuhan in 2019 and results in Covid-19 disease. It has now affected more than 216 countries and has resulted in nearly 4 million fatalities so far. There is a bidirectional association between Covid-19 and diabetes. Diabetes is one of the important comorbid conditions which adversely affects the outcomes after Covid-19 disease. Covid-19, in turn, can result in new-onset diabetes (NOD) due to specific mechanisms beyond those contributing to stress hyperglycaemia. In this editorial, we review the important facts regarding this bidirectional relationship between Covid-19 and diabetes. We stress the need for screening for undiagnosed hyperglycaemia present at admission or during the course of the disease. Finally, management of hyperglycaemia provoked or exacerbated by steroid therapy is another crucial aspect that needs attention.

Bidirectional relation between diabetes and Covid-19

Diabetes is associated with poor outcomes in individuals affected by Covid-19. Diabetes was found to be present in 11.5% of individuals with Covid-19.[4] Diabetes results in severe Covid-19 (risk ratio [RR] of 2.45), poor composite outcome (RR 2.38), mortality (RR 2.12), and adult respiratory distress syndrome (ARDS; RR 4.64).[5] Further, patients with poorly controlled diabetes (HbA1c of 10.0% or higher) have worse outcomes (increased Covid-19-related mortality with HR of 2.23 in type 1 diabetes and HR of 1.61 in type 2 diabetes) compared to those with acceptable glycaemic control (HbA1c of 6.5%–7.0%).[6] Of the 2000 Covid-19 deaths reported from India, 96% of the cases were recorded as having comorbid conditions.[7] Most common comorbid conditions included diabetes (66%), hypertension (54%), coronary artery disease (18%), and chronic kidney disease (15%).[7] Diabetes may increase susceptibility to SARS-CoV-2 infection, but data to support or refute this are lacking.[8] Newly recognized hyperglycaemia is associated with more severe Covid-19 disease and poor outcomes than previously diagnosed individuals with diabetes. Bode *et al*. found mortality rates of 41.7% (40/96) in newly diagnosed diabetes compared to 14.8% (13/88) in those with pre-existing diabetes.[9] There are limited data on NOD after Covid-19. One retrospective cohort study found NOD rates that were 1.5 (1.4–1.6) times than seen in the matched control group.[10] In another retrospective cohort study among 193 113 Covid-19 patients aged ≤65 years, NOD was the sixth most common post-acute clinical sequelae over a median follow-up of 2.9 months.[11]

Covid-19 is associated with a surge in hyperglycaemic emergencies. In a systematic literature review which included 71 patients of Covid-19, diabetic ketoacidosis (DKA) was present in 45 (63.4%), euglycaemic DKA in 6 (8.5%), combined DKA/HHS

(hyperglycaemic hyperosmolar non-ketotic syndrome) in 19 (26.8%), and HHS in 1 (1.4%).[12] In another systematic review, 77% of patients with Covid-19 who developed DKA had type 2 diabetes mellitus.[13] Another complication is mucormycosis, which has risen more rapidly during the second wave than the first wave of Covid-19 in India, with at least 14 872 cases by 28 May 2021.[14] Uncontrolled blood glucose is one of the substantial risk factors responsible for it.

Possible mechanisms responsible for bidirectional relationship between Covid-19 and diabetes mellitus

Due to impaired innate and adaptive immunity in diabetes, the ability to fight infections is decreased. Dysregulated immune response may predispose them to cytokine storm in Covid-19. Expression of angiotensin-converting enzyme 2 (ACE2) receptor, which facilitates entry for SARS-CoV-2, is increased in patients with diabetes.[15] This may explain the increased severity of Covid-19 in these patients. SARS-CoV-2 infection can enhance insulin resistance in addition to impairing insulin secretion. ACE2 converts angiotensin II (Ang II) into angiotensin (1–7), thus regulates blood pressure, decreases oxidative stress, and increases the activity of glucose transporter 4 (GLUT4).[16] However, during Covid-19 infection, ACE2 expression is decreased and this results in an exaggerated activity of Ang II with subsequent insulin resistance (by serine/threonine kinases activation), oxidative stress, inflammation and hypertension.[17] These mechanisms can result in new-onset or worsening of pre-existing hyperglycaemia in Covid-19, in addition to that consequent to stress hyperglycaemia, as seen with other infections or inflammatory conditions, and the use of glucocorticoids. Entry of SARS-CoV-2 into pancreatic islets is also mediated by ACE2 that can damage pancreatic beta cells.[18] According to Tang *et al*., SARS-CoV-2 infection can lead to beta cells trans-differentiation resulting in lower insulin expression and higher production of glucagon.[19] This beta cell destruction may result in NOD during acute phase or post Covid.

Screening for hyperglycaemia during admission in a Covid-19 facility

Given the importance of recognizing and treating hyperglycaemia, every patient with Covid-19, especially those hospitalized, should be screened for high glucose levels at admission and periodically after that during the hospital stay. This can be done through a blood glucose meter with a reading taken at admission or values taken in relation to meals. Wherever feasible a fasting plasma glucose and HbA1c measurement should also be done in the laboratory. If blood glucose level is ≥250 mg/dl then blood or urine should be checked for the presence of ketones. As each measurement has its pitfalls, combinations of different measurements decrease the chances of missing patients with hyperglycaemia. We have proposed a strategy in detail and the recommended cut-offs for diagnosis of hyperglycaemia requiring further action in an individual without known prior diabetes in our earlier publications.[20,21]

Management and prevention

Poor outcome in Covid-19 can be avoided with timely diagnosis and optimal management of hyperglycaemia in these patients. Insulin therapy is preferred in hospitalized patients. Basal-bolus regimen (three injections of prandial and one or two injections of intermediate/long-acting insulin) or basal-plus regimen (prandial injection(s) for the meal(s) with more than desired postprandial excursion and basal injections) provides the flexibility of dose titration.[22] Therefore, it is more effective and safe than pre-mix insulin or oral glucose-lowering agents. Continuous intravenous insulin infusion is preferred in individuals with severe hyperglycaemia despite using basal-bolus insulin, critical care illness like sepsis with or without shock or hyperglycaemic emergencies. The use of glucocorticoids further increases the requirement of the dose of insulin (units/day). A basal-bolus regimen should be preferred, especially those receiving twice daily intermediate acting glucocorticoids (e.g. methylprednisolone). Those who are newly diagnosed with hyperglycaemia and are receiving a single daily dose of intermediate-acting glucocorticoid may benefit from a single shot of prandial insulin before lunch and intermediate-acting insulin in the morning hours, as these patients have disproportionately high blood glucose values in the afternoon and evening hours (before lunch, after lunch and before dinner). Since severe Covid-19 disease is associated with poor baseline HbA1c, ensuring good glucose control in all patients with diabetes is critical for optimal outcomes for individuals and the healthcare system.

Summary

Diabetes and Covid-19 have shown a bidirectional association with increased disease severity in patients with diabetes and poor blood glucose control due to Covid-19 infection. Screening for hyperglycaemia at the time of admission and regular blood glucose monitoring must be done in all patients. Management protocols for hyperglycaemia are available and should be implemented to improve outcomes in patients with Covid-19. There should be preparedness for the next wave, and preventive measures should be vigorously implemented, especially for blood glucose control. There is a need for vaccination, and frequent follow-up to ensure good glycaemic control, management of comorbid conditions and post-Covid complications (if any).

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