

COVID 19 and diabetes: An endocrinologist's perspective

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ABSTRACT

The clinical manifestation of COVID-19 is diverse, oscillating from mild flu-like symptoms to more severe outcome, such as acute respiratory distress syndrome, multiple organ failure, and death. Advanced age and comorbidities, such as diabetes mellitus, high blood pressure, and history of cerebrovascular accidents are reported to have worse outcome. Chronic inflammation by cytokine storm and direct insult to pancreatic by COVID-19 might be postulated mechanisms of inducing or deteriorating diabetes. Individualized patient-centric treatment and optimal blood sugar control should be made based on disease severity, presence of comorbid condition, and complications related to diabetes, age, and other risk factors. Recent clinical trials have shown some hope to anti-interleukin antibody as a potential therapeutic option against COVID-19 especially in people with severe illness.

Keywords: Acute respiratory distress syndrome, angiotensin-converting enzyme 2, COVID-19, cytokine storm, diabetes

Introduction

Corona viruses are implicated for a number of communities acquired infection, such as Middle East Respiratory Syndrome (MERS), severe acute respiratory syndrome (SARS), and the novel corona virus now officially named SARS-CoV-2, is the causative agents corona virus disease (COVID-19) disease outbreaks.^[1]

COVID-19 is a highly contagious disease with human to human transmission; has more mortality in compare to influenza (9 3.75 vs 1%), hence need prompt action to contain it.^[2] The most common symptoms observed in COVID-19 illness are fever (99%), fatigue (70%), dry cough (60%), myalgia (44%), and dyspnea. Respiratory failure from acute respiratory distress

syndrome (ARDS) is the leading cause of mortality. Elderly patients with underlying co-morbidities including hypertension, diabetes is more likely to have adverse outcomes.^[3]

Among the various non-communicable disease; type 2 diabetes mellitus (T2DM) looks to be a risk factor and poor prognosis for acquiring the COVID-19 infection.^[1,2] Although T2DM poses more risk of severe symptoms and mortality in many viral infections, there are some unique mechanism operate in COVID-19 infections that need a special discrete consideration, which will have clinical outcome for better management of badly affected patients.

Immunity, Diabetes, and COVID-19

Patients with diabetes have both compromised innate and acquired immunity.^[4] Fasting hyperglycemia and diabetes are independent predictor of morbidity and mortality in SARS.^[5] Elderly, metabolically compromised patients are risk for COVID-19 infections and more susceptible to high virus loads. They have a dysregulated cytokine/chemokine

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response and prone for cytokine storm. The characteristics of cytokine storm in severe COVID-19 are increased levels of chemokines (C-C motif chemokine ligand (CCL)-2, CCL-3, and CCL-5), tumor necrosis factor, and proinflammatory cytokines interleukin (IL)-1 β , IL-6 along with low levels of the antiviral factors such as interferons.^[6]

T2 DM with severe COVID-19 infection are more prone for a cytokine storm characterized by increased titer of inflammatory cytokines IL-2R and IL-6 and chemokines.^[7] ARDS, an immunopathological changes in lungs and multi-organ failure leading to increased fatality, is due to the consequence of poorly regulated inflammatory cytokine storm.^[7]

Diabetes Increases Morbidity and Mortality in COVID-19 Corona Virus and ACE2

From endocrine perspective, COVID-19 seems more severe in patients with diabetes.^[1] COVID-19 virus enters human cells by attaching to the angiotensin-converting enzyme 2 (ACE2).^[7,8] In the lungs, COVID-19 after binding to its functional receptor ACE2 enter primarily type II pneumocytes;^[9] followed by downregulation of surface ACE2, resulting in unopposed angiotensin II accumulation. It is reported that the renin–angiotensin–aldosterone system gets activated locally, this may mediate lung injury responses to viral insults.^[9]

The liver and in the pancreatic β - cells express ACE2.^[8] The possible underlying mechanism that cause acute surge of hyperglycemia, and transient T2DM could be direct damage to the pancreatic β - cells by binding with ACE2 protein leading to decrease insulin secretion and development of insulin resistance by entry into the liver during the acute infection.^[8]

Angiotensin-II (AngII) is produced from Angiotensin-I by angiotensin converting enzyme (ACE) in the lungs. AngII cause vasoconstriction of vessels, pro-oxidative, and pro-inflammatory effects through acting at AngII receptor type 1 (AT1). Angiotensin 1-7 (Ang1-7) is produced when ACE2 act upon AngII, which binds Mas receptor (MasR) mediates anti-oxidative and vasodilatory anti-inflammatory affects.^[10] It is assumed that binding to ACE2 by COVID-19 may attenuate activity of remaining ACE2, further awry the ACE/ACE2 balance to a state of predominant ACE/AngII/AT1 axis signaling, in which AngII causes inflammatory pulmonary vasoconstriction and oxidative organ damage.^[11] This assumption can be extrapolated as Liu *et al.*, demonstrated that COVID-19 infected patients have higher serum AngII levels, viral load, and lung injury than in non-infected.^[11,12] It is hypothesized that patients with fatal COVID-19 infection may cause an increase in the activation of predominant ACE/AngII/AT1 axis signaling, particularly in T2DM, insulin-resistant states, and hypertension.^[7] Poorly controlled diabetes leads to more glycation of ACE2 with reduced ACE2; this could explain the increased susceptibility to severe lung damage and ARDS with COVID-19.^[13]

There is paucity of evidence in patients with diabetes with COVID-19. Fang *et al.* has recently documented 15-20% increase in severity and morbidity of COVID-19 infected diabetes patents in three different study from China.^[14] Analysis of data from 11 studies regarding laboratory abnormalities in patients with COVID-19 did not describe elevated blood glucose or diabetes as predictor of severe disease.^[15]

Reported data from an epidemiological study by Chinese Centre for Disease Control and Prevention consisting of 72,314 COVID patients described increased mortality in people with diabetes (7.3%, patients with diabetes 2.3%, overall).^[16] Study by Wang *et al.* showed that patients admitted in intensive care unit (ICU) with corona virus infection were more than 3 times likely to have underlying diabetes than non-ICU patients.^[17]

Responsibility of primary care physician to prevent COVID-19 infection in the diabetics

The primary care physicians have paramount responsibility as they are the initial contacts of their patients in the prevention of COVID-19 infection because of their close long-term association and patient trust they enjoy. Some basic general preventive measures to be followed are depicted below.^[18]

- I. Simple measures should be taken to avoid infection from the virus
- II. Frequent hand rubbing with alcohol-based sanitizer or readily available soap and before eating and after being in public place
- III. Sharing of foods, glasses, and towels among ourselves should be avoided
- IV. Utmost care should be taken not to have contact with someone is febrile or having flu like illness
- V. Health-care personals to be informed promptly if someone ill with respiratory symptoms
- VI. Mouth and nosed to be covered with tissue or crook of the elbow. Tissue should be discarded properly
- VII. Avoid contact with wildlife and farm animal
- VIII. Unnecessary travel to the major hot spot should be avoided
- IX. It is advisable to diabetic patients to keep good amount of insulin vials and refills and oral diabetic drugs with them.

What primary care physicians can do if they suspect COVID-19 in the diabetic patient?

Based upon the initial symptomatology of COVID infection, the primary care physician must take immediate and appropriate steps to prevent patient from worsening. As such diabetic population is at higher risk of rapid downhill course once COVID infection sets in. Patients with diabetes and COVID-19 infection should follow several protective measurements.^[18]

- I. To notify the appropriate health-care authority with clinical suspicion for COVID-19, as screening of covid-19 is available at specific designated center
- II. Quarantine the suspected case for 14 days or until symptoms resolve

- III. Adequate hydration to be maintained and treatment for fever and cough to be treated appropriately
- IV. “Sick day rules” should be followed as for any emergency or stressful situation to improve their diabetes control and related complication. If someone is on insulin regular checking ketone bodies, blood glucose level to maintain euglycemic state, and adjust insulin dose accordingly
- V. When patients get admitted to hospital due to uncontrolled blood sugar. Monitoring blood glucose and to stop the use of oral diabetic agents, especially metformin and sodium-glucose cotransporter-2 inhibitors (i.e. empagliflozin), as in this situation is insulin is recommended
- VI. If the patient develops any life-threatening complication, such as ketoacidosis (DKA) or any systemic infection, must be hospitalized for prompt treatment as an emergency.

Recent Drug Development Targeting Inflammation Could Help Treat COVID-19 in Diabetes

Guo and colleagues^[1] have reported that patients with diabetes has more elevated levels of cardiac, renal and liver enzymes than the patients without diabetes, indicating injury to these vital organs, some of them are predisposed to multiple organ failure.

COVID-19 infected diabetes patients have increased markers of inflammation, especially IL6 is responsible for inducing the cytokine storm. The anti-IL-6 chimeric monoclonal antibody siltuximab; (Siltuximab In Serious COVID-19) SISCO study, in COVID-19 patients who have developed serious respiratory complications has shown efficacy of IL-6 inhibition.^[19] In some Italian centers off-label the use of monoclonal antibody against the IL-6 receptor, tocilizumab has been shown positive results in patients with COVID-19; it is also recently being tested as an *ad hoc* randomized controlled trial.^[8] Additionally, the new Janus Kinase inhibitors drugs, like upadacitinib, baricitinib, tofacitinib, could novel approaches to deal against COVID-19 subjects, mostly with diabetes subjects that might inhibit both inflammation and cellular viral entry in COVID-19.^[2,8]

Conclusion

It is now clear that COVID-19 infection is confined to respiratory system and complications are associated in all vital organs. People with comorbidities are especially vulnerable to the complications of COVID-19. There is recent surge of publications on COVID infection mostly from one region of China and hence generalization of the finding may not be possible because of paucity of data from other parts of the world. The present commentary focusses primarily on how to clinically examine and manage diabetes in the current COVID pandemic. It is expected that with availability of more credible data, the guidelines will be further refined and the management will become simpler.

Learning points

1. Diabetes patients with COVID-19 infection are more prone for increased mortality, ICU admission, and prolonged hospital stay compared to their non-diabetic counterparts
2. COVID-19 with diabetes need strict glycemic control with insulin, and oral diabetic agents should be avoided when admitted to ICU
3. Diabetic patients should keep their blood sugar under control by doing frequent monitoring using digital appliance and to contact with their physician to remain in good glycemic control.

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Conflicts of interest

There are no conflicts of interest by the authors to declare.

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