

Diabetes Mellitus and COVID-19 : A Short Communication

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Abstract

The Corona Virus Disease 2019 (COVID-19) pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has affected millions of people globally with a higher rate of mortality in patients with Type 2 Diabetes Mellitus (T2DM). Several mechanisms have been suggested for the severity of COVID-19 illness in patients with diabetes including increased virus entry, decreased viral clearance, diminished T-cell function, increased susceptibility to high levels of inflammation and cytokine storm. Hyperglycemia and severe COVID-19 have been shown to have a bidirectional relationship. Hyperglycemia, even in the absence of diabetes, can lead to increased susceptibility for the infection as well as increased severity of COVID-19. In addition, patients with severe COVID-19 may exhibit extreme levels of hyperglycemia or new-onset diabetes, which has been associated with worse outcomes. Some recent data have also suggested a link between outpatient glycemic control (prior to the infection) and severity of COVID-19. The available evidence suggests that improved glycemic control, both prior to infection as well as during hospitalization, are important measures in reducing the risk of severe COVID-19.

Keywords: COVID-19 • Diabetes mellitus • Insulin resistance • Hyperglycemia

Introduction
The Corona virus disease 2019 (COVID-19) pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been ongoing since early 2020 and has affected millions of people globally with a high rate of mortality. Diabetes (mostly Type 2 Diabetes Mellitus, T2DM) is among the major co-morbidities leading to poor outcomes in patients afflicted with COVID-19. In our previous review of the topic, we explored potential mechanistic links that could explain the observed higher morbidity in this patient population[1]. We suggested that patients with T2DM with insulin resistance and other co-morbidities have a state of chronic inflammation which can be greatly exacerbated with a hyper-immune response (cytokine storm) during the COVID-19 illness that could lead to increased severity of the disease. In this commentary, we re-emphasize the underlying mechanisms, describe new evidence, and discuss the effect of glycemic control (both prior and during the infection) on outcomes of patients with diabetes and COVID-19.

Interrelationships between Diabetes, Hyperglycemia and Severity of COVID-19

It is well known that patients with diabetes and hyperglycemia are at increased risk for various bacterial, fungal and viral infections. A bidirectional link between chronic inflammation and hyperglycemia is known to be of importance in the development and progression of chronic complications of diabetes. It has also been suggested that hyperglycemia can lead to an elevated expression

of ACE2 (the cellular “receptor” for the SARS-CoV-2) in lungs and other tissues that can lead to increased viral entry. Also, with hyperglycemia, there is increased concentration of glucose in the airway secretions, and exposure of pulmonary epithelial cells to elevated glucose is associated with increased replication of influenza virus and infection[2]. Similarly, hyperglycemia appears to increase the replication of SARS-CoV-2 in monocytes, which might explain the prolonged recovery of COVID-19 in patients with diabetes[3]. In addition, some patients with severe COVID-19 illness exhibit extreme levels of hyperglycemia, and such extreme hyperglycemia, even in the absence of known diabetes, has been associated with poorer outcomes of COVID-19[4,5].

The many co-morbidities that are present in patients with diabetes including Hypertension (HTN), obesity, Dyslipidemia (DLD), cardiovascular disease and insulin resistance can collectively contribute to increased severity of COVID-19[1]. HTN can lead to increased angiotensin-2, leading to worsening of infection, ARDS, and increased risk for adverse outcomes[1,6,7]. Obesity can cause impaired breathing mechanics and gas exchange, leading to difficult respiratory support in patients with COVID-19. And, dyslipidemia, especially elevated free fatty acids directly activate Toll-Like Receptor 4 (TLR4), which leads to cytokine secretion and a more severe inflammatory response[1]. Hence multiple mechanisms can increase the severity of COVID-19 in patients with diabetes including increased virus entry, decreased viral clearance, diminished T-cell function, increased susceptibility to high levels of inflammation and cytokine storm [1,8].

Effect of Outpatient Glycemic Control on Severity of COVID-19

There is ample evidence suggesting that patients with diabetes and/or hyperglycemia tend to have poorer outcomes when afflicted with COVID-19. Some recent data has suggested a link between outpatient glycemic control (prior to the infection) and severity of COVID-19. Two large studies from the U.K. in patients with diabetes and COVID-19 found that high HbA1c levels was associated with increased mortality, suggesting that pre-infection glycemic control may have an important role in COVID-19 outcomes[9,10]. In contrast, a smaller study from France did not find an association between long-term glycemic control and COVID-19 outcomes[11]. Although the relationship between outpatient glycemic control and severity of COVID-19 has not been entirely settled, good glycemic control could potentially reduce morbidity and mortality from COVID-19.

Various newer diabetes medications, including Glucagon Like Peptide-1 (GLP-1) agonist and Sodium-Glucose co-Transporter-2 (SGLT-2) inhibitors not only improve glycemic control, but promote weight loss and improve insulin resistance. The association of the outpatient use of any specific glycemia-lowering agent and COVID-19 has not been extensively studied. Never the less, in a recent study, outpatient use of metformin and SGLT-2 inhibitors was associated with less severe COVID-19[12]. It should be noted, however, that an expert panel has recommended against the continuing the use of SGLT-2 inhibitors in COVID-19 patients due to potential dehydration and euglycemic Diabetic Ketoacidosis (DKA)[13].

Extreme Hyperglycemia in COVID-19

Extreme hyperglycemia including DKA and Hyperglycemic Hyperosmolar State (HHS) requiring high doses of insulin has been observed in patients with or without pre-existing diabetes in patients with COVID-19 [14]. Possible mechanisms leading to extreme hyperglycemia in individuals with no prior history of diabetes include high levels of inflammation and cytokine activation (especially IL-6) and use of glucocorticoids for treatment of COVID-19 all of which can lead to insulin resistance; there may also be a significant decrease in insulin production and secretion by direct viral destruction of beta cells of the pancreas due to virus entry through ACE2 expression on their cell surface[15]. However, it is not yet certain whether these acute changes persist long-term or are transient. Similar mechanisms can also lead to DKA in patients with pre-existing or new-onset type 1 and type 2 diabetes. Given the increased insulin resistance and insulin deficiency state (due to beta cell malfunction), high doses of insulin are required to maintain euglycemia in these severely ill patients. It should be noted that in addition to extreme hyperglycemia, large fluctuations in glycemic levels during the first week of hospitalization are associated with increased mortality in patients with COVID-19[5].

It is also generally advised that insulin therapy should be the mainstay of treatment in patients with hyperglycemia and COVID-19. The DARE-19 Phase III trial evaluated the safety and efficacy of SGLT-2 inhibitor use in patients hospitalized with COVID-19; the results showed no superiority in early recovery or mortality at 30 days[16].

Conclusion

T2DM along with the underlying insulin resistance can lead to increased severity of COVID-19. Based on the available evidence, improving glycemic control, both prior to infection as well as during hospitalization, is an important measure in reducing the risk of severe COVID-19. In addition, it is important to monitor glucose levels for new-onset diabetes in patients with COVID-19. Finally, insulin remains the mainstay of therapy for control of hyperglycemia during hospitalization in patients with COVID-19.

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