Diabetes and COVID-19: A Tale of 2 Pandemics

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This Commentary relates to the article by Anastasiou et al on pages 12–19.

Sebastian Junger's book "The Perfect Storm" describes a combination of unfortunate events, leading to a tragedy at sea for the fishing vessel *Andrea Gail*.[1] Analogously, communities worldwide are faced with the unleashing of a virulent and contagious infection on a background of increasingly widespread metabolic factors created by modern living. Individual and public health trends caused by sedentary and calorie-rich lifestyles are contributing to vast increases in obesity, metabolic syndrome, and glucose intolerance. The latter factors by themselves are the reasons for diabetes to be designated as a major public health issue by the WHO,[2] and future predictions for the global diabetes burden are nothing short of dire. In this prevailing atmosphere of chronic but simmering unhealthy trends in public health, the SARS-CoV-2 has found fertile ground to gain a lethal foothold. Beyond doubt, gathering evidence clearly points to the combination of diabetes and COVID-19, resulting in potentially devastating consequences in morbidity and mortality.[3]

Why the particularly adverse impact of the coronavirus on metabolic derangements in individuals with diabetes? The knowledge and evidence is evolving rapidly. Infection with COVID-19 may worsen glucose tolerance acutely, leading to severe hyperglycemia, ketoacidosis, and life-threatening presentations.[3] Clinical outcomes in patients with diabetic who suffer superimposed COVID-19 infection are almost uniformly worse than in nondiabetic persons.[4] At the mechanistic level, the lower glucometabolic reserve and cardiovascular milieu in diabetes predisposes to lower defenses, weaker immunity, harmful cytokine and inflammatory responses, and poor maintenance of organ-system functions.[5] In other words, the coronavirus has found diabetes to be a willing partner for inflicting damage to the health and well-being of the human host in ways that we are only beginning to understand.

Fortunately, in this atmosphere of apparent hopelessness, there might be cause for optimism. The last quarter century has witnessed quantum leaps in advancements in glucose monitoring and diabetes pharmacotherapy. An array of innovations has produced therapeutic options that were nonexistent only a few decades ago. Understanding the pathophysiology of diabetes has enabled us to develop targeted therapies, which may be used in a multipronged manner, and individualized to the patient's unique disease situation. Clearly, the common factor in all the available antihyperglycemic classes of medications is their efficacy in glucose-lowering and, in some cases, beneficial impact on comorbidities and complications. However, as patients with diabetes are encountering the SARS-CoV-2 virus, the potential modulating effect of the diabetic medications on their clinical course is likely manifested and, slowly but surely, becoming understood. Plowing through this quagmire of information to identify trends and patterns has undoubtedly been no easy task.

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The enormity of information and the rapidly changing scenarios in the hospital setting as well as ambulatory care has created confusion at times.

On the bright side, knowledge from the frontlines has been a ready source of data that has armed clinicians and investigators to study and apply the evidence for the benefit of patients. In this regard, the role of diabetes treatments such as insulin, metformin, sodium-glucose transport protein 2 inhibitors, and incretin-based therapies (IBTs), ie, glucagon-like peptide-1 receptor agonists (GLP1-RAs) and dipeptidyl peptidase-4 inhibitors, in COVID-19 infection, particularly in influencing the course of illness, has generated keen interest.[6] It is understood that insulin therapy has been the mainstay for maintaining optimal glucose control in the frequently fulminant hyperglycemia and acute decompensation seen in patients with COVID-19, either with or without a history of diabetes. Intravenous and intensive multiple daily insulin injection regimens have been particularly effective, and various organizations, institutions, and health care systems have established guidelines customized to the specific clinical situation.[7] The role of traditional therapies, such as the sulfonylureas and metformin, has been studied as well.

However, it is in the realm of the more recently introduced pharmacologic agents that IBTs have been hypothesized to exert beneficial effects on COVID-19 outcomes because of anti-inflammatory properties, and furthermore, dipeptidyl peptidase-4 receptors have been found to have interactions with the SARS-CoV-2 virus; insights into receptor-mediated actions have led to postulated mechanisms that could explain the potential benefits of IBTs in COVID-19.[8] In addition to improving hyperglycemia, IBTs may confer additional protection against the short-term and long-term consequences of COVID-19. Although there are intensive debates regarding safety of different classes of antidiabetics at the advent of COVID-19, multiple ongoing studies are evaluating the adjuvant role of various antidiabetic agents such as IBTs in reducing the severity of COVID-19. Dapagliflozin, an SGLT-2 inhibitor, has been a recent addition to the trend, and the present article is an accompanying editorial of the interesting review made by Anastasiou and coauthors on dapagliflozin and COVID-19 progression in high-risk patients with or without diabetes, where they lay out the evidence for the cardioprotective and nephroprotective effects of this medication and discuss the potential favorable impact of dapagliflozin on COVID-19 and its complications.[9]

There is strong evidence that subjects with cardiovascular or kidney diseases who contract COVID-19 have a worse prognosis than those without these underlying conditions. Therefore, it is mandatory to preserve the integrity of the renal and cardiovascular system in patients with type-2 diabetes affected by SARS-CoV-2.[4] GLP1-RAs and sodium-glucose transport protein 2 inhibitors have proven cardio-renal-metabolic benefit; in this context, Anastasiou and coauthors[9] discussed the DARE-19 (Dapagliflozin in Respiratory Failure in Patients With COVID-19) trial, designed to investigate the impact of dapagliflozin on COVID-19 progression. However, trial results did not achieve statistical significance for the primary endpoints of prevention of organ dysfunction, reduction in all-cause mortality, and improvement in the clinical status (ranging from early recovery to death) at 30 days.[10] It has been shown that the duration of lockdown and social distancing measures are directly proportional to the worsening of glycemic control and diabetes-related complications, possibly through aggravation of overweight and obesity. The importance of GLP1-RAs use in the prevention of weight gain is relevant in this regard.[8] In addition, GLP1-RAs have demonstrated significant anti-inflammatory and antiadipogenic effects, partly through decreasing insulin resistance—actions that could potentially be beneficial during COVID infection.[8]

The French-Algerian philosopher and writer Albert Camus, in his prophetic work "The Plague," describes the ravages of a rat-borne contagion on the population of a fictitious town as seen through the eyes of the physician-narrator.[11] After the catastrophe has past, the chilling ending notes that "…the plague bacillus never dies or disappears for good; that it can lie dormant for years…," ready to resurface when the opportunity arises. Likewise, the current situation, a daunting overlap of an inexorably worsening metabolic disease and a mysterious infection, is not likely to be humanity's last encounter with a figurative bacillus. Surely, the double health risk of diabetes and COVID-19 infection in modern times is a unique challenge for clinicians and researchers alike. The rapidly evolving fund of knowledge and evidence regarding antidiabetes medication use in these settings behooves us to put all the pieces of the puzzle together in a safe and expeditious manner for the benefit of our patients.

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