# COVID-19 and Diabetics

This is a dangerous combination.

BY WINDY COLE, DPM

High plasma glucose as seen in diabetes mellitus is a known risk factors for increased susceptibility to infection. Evidence-based reports continue to add credence to the belief that the comorbid state caused by diabetes increases the morbidity and mortality in persons contracting the coronavirus. Elevated awareness of the clinical features, pathophysiology, and potential mechanisms of action that contribute to the added risk in patients with diabetes is needed. In this article we will discuss the challenges faced by persons with diabetes and clinicians providing their care during the COVID-19 pandemic. This information will allow clinicians to provide appropriate care while spurring new investigations to better mitigate coronavirus infections in this at-risk patient population.

Background on COVID-19

The World Health Organization (WHO) has declared the COVID-19 outbreak to be a public health emergency of global concern. COVID-19 is caused by a novel coronavirus known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) and has rapidly spread across the world.[1] (Figure 1) The dissemination mechanism of the virus is primarily via transmission of respiratory droplets between people.[1] The incubation time is on average 6–8 days, followed by 1–2 weeks of symptomatic disease. The majority of COVID-19 positive patients present with symptoms of an acute respiratory illness including fever, body aches, lethargy, dry cough, and breathing difficulties, although it appears that the novel coronavirus may be impacting more than just the lungs, especial-

RED COUNTRIES WITH 100 OR MORE CONFIRMED CASES.
BEIGE COUNTRIES WITH FEWER THAN 100.
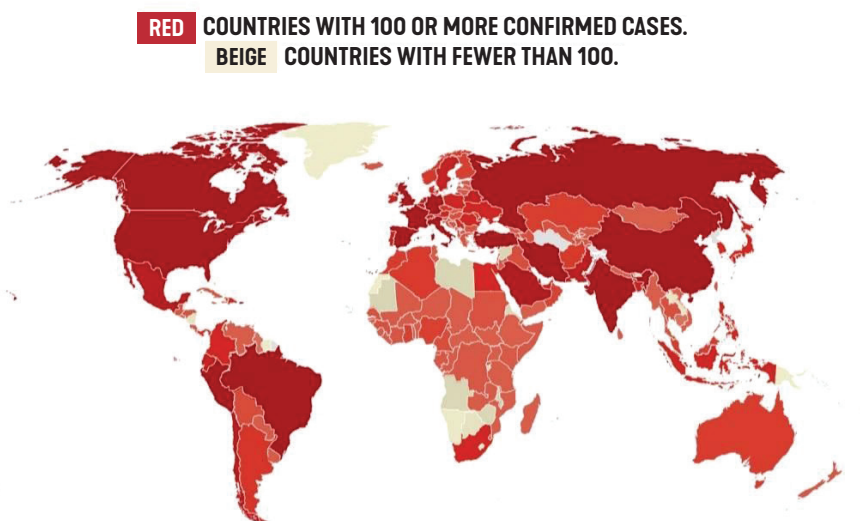
SOURCE: WHO, CDC, NHC, AND OTHER SOURCES VIA WORLDOMETER

Figure 1: SARS-CoV-2 virus mechanism of cell entry via the ACE2 receptor.

> **Clinicians from around the globe have reported kidney damage, liver dysfunction, heart problems, and most recently, issues with blood clots such as deep venous thrombosis (DVT).**

ly in severe cases. Clinicians from around the globe have reported kidney damage, liver dysfunction, heart problems, and most recently, issues with blood clots such as deep venous thrombosis (DVT). In the most severe cases, coronavirus infection can lead to death.[2-8] A proportion of patients infected with COVID-19 are asymptomatic or exhibit only mild symptoms, but remain equally infectious.[2-8] As is true for so many aspects of the COVID-19 pandemic, information on clinical complications caused by this virus continues to evolve.

Diabetes in the US

Diabetes mellitus is one of the leading causes of morbidity and mortality world-wide and the number of newly diagnosed cases is on the rise. In 2018, a crude estimate of new cases of diabetes among adults 18 years old and older in the US was 1.5 million—or 6.9 per 1,000 persons.[9] This same survey estimated that 34.1 million—13.0% of all US adults aged 18 years or older, had either diagnosed or undiagnosed diabetes in 2018.[9] Among those aged
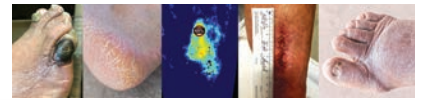
65 years or older, a population at higher risk for death from COVID-19, 26.8% have DM.[9] Diabetes mellitus is a metabolic disease characterized by impaired glucose metabolism resulting in higher than normal glucose levels in the body. This condition occurs due either to cells failing to produce insulin or lacking the response to insulin, or both.

This increasing pervasiveness of diabetes among Americans has had deleterious effects on the overall costs of healthcare, as well as on society and the economy. After adjusting for inflation, medical costs of diabetes in the United States increased by 26% from $188 billion in 2012 to $237.3 billion in 2017, due to the increased prevalence of diabetes and the increased cost per person with diabetes.[10] Historically, persons with diabetes have exhibited increased risk and susceptibility to infectious disease such as Staphylococcus aureus and Mycobacterium tuberculosis likely due to compromised immunity.[11] Individuals with diabetes mellitus, hypertension, and severe obesity

> **Since the beginning of the coronavirus pandemic, health officials have cautioned that people with diabetes are at risk of developing severe symptoms of COVID-19.**

(BMI $\geq$ 40 kg/m^2) are also more likely to be infected and are at a higher risk for complications and death from COVID-19.[12]

The Pathophysiology of SARS-CoV-2

COVID-19, also known as SARS-CoV-2, shares 80% genetic identity to SARS-CoV and 50% identity to the MERS-CoV, both viruses which originate in bats and can infect humans and other animals.[13] The entry of SARS-CoV-2 entry into the body is a complex process. The initial step involves the virus binding to cell surfaces via the angiotensin converting enzyme 2 (ACE2) receptor.[14] ACE2 is a protein on the surface of many cell types including tissues of the lungs, heart, blood vessels, kidneys, liver, and GI tract. ACE2 is very abundant in the epithelium of the nose, mouth, and lungs-the common sites for coronavirus entry.

Like a key inserted into a lock, the virus fuses to cell surfaces (Figure 2). This protein provides the entry point for the coronavirus to hook into and infect a wide variety of human cells.[15] ACE2 plays a critical role in regulating processes such as blood pressure, wound healing, and inflammation. When SARS-CoV-2 binds to the ACE2, it prevents it from performing its normal functions, thus leading to increased inflammatory responses causing tissue injury and necrosis, especially in the lungs and heart.
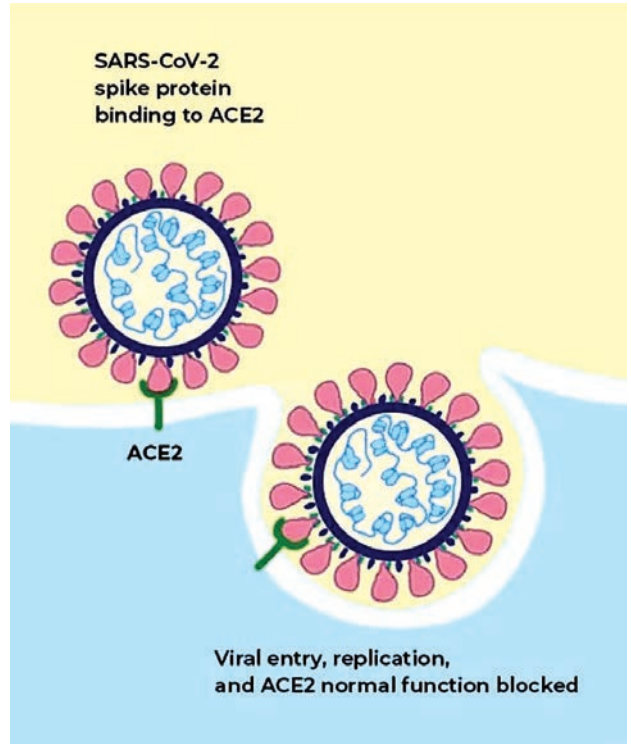

Figure 2: A map depicting the global spread of the coronavirus.

The CORONADO Study

Since the beginning of the coronavirus pandemic, health officials have cautioned that people with diabetes are at risk of developing severe symptoms of COVID-19. A recent study published in *Diabetologia* appears to justify this warning. This study was the first of its kind to specifically research the effect of diabetes on patients hospitalized with COVID-19.[16] The publication on "COVID-19 and Diabetes Outcomes", thus coined the CORONADO study, involved analysis of 1,317 subjects admitted to 53 public and private French hospitals between March 10 and March 31, 2020. Across all subjects in this study, one in ten patients had died within seven days of hospital admission, while one in five had been mechanically intubated. It should be mentioned that only 18% of subjects were able to be discharged to home by day 7. The majority of the subjects (89%) had type 2 diabetes. Interestingly, in 3% of these cases, the diagnosis of diabetes first occurred during hospitalization for COVID-19. Two thirds of the study subjects were men and the median age was 70 years.

Surprisingly, poor glycemic control was not associated with poor patient outcomes; however, the presence of systemic complications of diabetes, advanced age, and increased body mass index (BMI) did increase the severity of COVID-19 infection and the risk of mechanical ventilation as well as elevate the mortality rate. The presence of microvascular or macrovascular complications more than doubled the risk of death at day 7. Microvascular complications were found in 47% of the study subjects and included retinopathy, neuropathy, kidney disease, and small vessel peripheral arterial disease.

THE DIABETIC **FOOT**

Macrovascular complications such as cardiovascular disease (heart disease and stroke) were present in 41% of study subjects. Patients 75 years and over were 14 times more likely to die than patient under the age of 55. Respiratory conditions such as obstructive sleep apnea almost tripled the risk of dying within the first week of hospitalization. Increased BMI was positively and independently noted to be associated with tracheal intubation, ventilation, and poor patient outcomes. The authors concluded that additional studies are needed to determine the link

> **Type 2 diabetes is widely believed to be a chronic low-grade inflammatory disease that contributes to wide-spread immune system imbalances.**

between obesity, metabolic complications, and the severity of COVID-19 infection with specific attention to fat mass distribution, insulin resistance, and inflammatory and immune profiles.

Why Persons with Diabetes are at an Increased Risk

It has been proven that elevated glucose levels and diabetes mellitus (DM) are known independent predictors for mortality and morbidity in patients with SARS.[17] Based on previous SARS research, several potential mechanisms have been theorized that may explain the increase in susceptibility for COVID-19 in patients with diabetes.

Potential mechanisms that may increase the susceptibility for COVID-19 in patients with DM include: higher-affinity cellular binding and efficient virus entry, decreased viral clearance, diminished T-cell function, increased susceptibility to hyperinflammation and cytokine storm syndrome, and increased presence of cardiovascular disease.[18] Impaired immunity seen in persons with diabetes is a result of diminished T-cell and macrophage activation.[19] Studies have shown that patients having poor glycemic control experience decreased immune response to viral infection as well as bacterial contamination in the lungs.[20]

The combination of these factors is the likely reason many patients with diabetes are at increased risk for morbidity when infected by COVID-19. A study by Yang et al. found that there is increased abundance of ACE2 protein found in islet cells when compared to exocrine tissues.[21] This study suggests that the novel coronavirus might cause damage to islet cells and, in fact, cause diabetes as was seen in 3% of the CORONADO subjects.[21] Viral infections can cause increases in blood glucose levels in patients with diabetes that will adversely affect long-term patient outcomes. Therefore, it would stand to reason that diabetes when combined with COVID-19 infection may make for a deadly combination.

THE DIABETIC **FOOT**

Type 2 diabetes is widely believed to be a chronic low-grade inflammatory disease that contributes to widespread immune system imbalances. Obesity is an independent risk factor for Type 2 diabetes.[22] Obesity-associated inflammation is a direct result of the activation of immunity cells in adipose tissue that are released locally as well as systemically. Therefore, obesity is a known risk factor for surgical-site infections, nosocomial infections, skin infections, and upper-respiratory infections. Persons displaying excessive abdominal obesity can also suffer from mechanical respiratory issues.

These mechanical changes reduce ventilation causing asthma-like symptoms such as dyspnea, wheeze, and airway hyper-responsiveness.[23] As you may recall, subjects in the CORONADO study that suffered from these conditions were three times more likely to die within the first week of hospitalization. It is believed that in this subset of patients there is a change in the secretion of adipokines and cytokines, resulting in an induced impaired immune response.[24]

Common late-stage complications seen in persons with diabetes include ischemic heart disease and peripheral arterial disease. These co-morbid conditions further contribute to patient frailty and susceptibility to complications from the novel coronavirus. In some severe cases, COVID-19 patients have been crashing hard and fast from cardiac episodes, which have led some clinicians to believe that these sudden arrests may have been precipitated by thrombolytic events. It is hypothesized that critically ill COVID-19 patients are developing a pro-thrombotic form of disseminated intravascular coagulation (DIC) that is putting them at increased risk for thrombotic events.
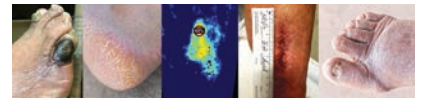
This growing concern is so common it has been recognized as a new pattern of clotting referred to as COVID-19 associated coagulopathy, or CAC.[25] The COVID-19 virus induces a hyper-inflammatory state. It has been suggested that systemic inflammation induces endothelial injury. This will activate the coagulation cascade and impair fibrinolysis with disruption of the endothelial barrier, and loss of physiologic antithrombotic factors which may elevate the risk for cardiac injury, heart failure, and decrease in circulation.

Lastly, early published data shows that the most common co-morbidities seen in patients with severe cases of COVID-19 are diabetes and hypertension. Angiotensin-converting enzyme (ACE) inhibitors are often used to treat both of these conditions. When patients are treated with ACE inhibitors, expression of ACE2 is increased. We have already discussed how the SARS-CoV-2 binds to cell surfaces via the ACE2 receptor. It has been suggested that the use of ACE inhibitors to manage diabetes could accelerate the entry of the novel coronavirus, thus amplifying the risk of serious disease and death.

Conclusion

Podiatric care remains vital during the current COVID-19 pandemic. Podiatric physicians provide es-

sential care to an at-risk patient population. Many of our patients have diabetes, predisposing them to greater complications from coronavirus infection. Steps must be taken to limit disruptions in care, including performing services in lower-risk settings to limit patient

> **Early published data shows that the most common co-morbidities seen in patients with severe cases of COVID-19 are diabetes and hypertension.**

morbidity and mortality. Through the implementation of a triage system to categorize the needs of our patients with diabetes, clinicians can continue to manage the care of our patients. Innovative therapies paired with alternative treatment sites of service such as telemedicine, home visits, mobile clinics, and free-standing office sites can help to mitigate risks for these vulnerable patients with advanced co-morbidities. By thinking outside the walls of the hospital, clinicians can continue to provide care to these at-risk patients while simultaneously reducing their risk of acquiring COVID-19 infection. Podiatric physicians can use advanced technologies such as virtual platforms, diagnostic imaging devices, and remote patient monitoring to find innovative ways to navigate this global healthcare crisis to benefit their patients and practices alike. **PM**

References

[1] Del Rio C, Malani PN. COVID-19-new insights on a rapidly changing epidemic. JAMA. 2020; doi: 10.1001/jama.2020.3072.

[2] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; doi: 10.1016/S2213-2600(20)30079-5.

[3] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; doi: 10.1056/NEJMoa2002032.

[4] Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; doi: 10.1111/all.14238.

[5] Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020; pii: S1201-9712(20)30136-3. doi: 10.1016/j.ijid.2020.03.017.

[6] Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020; doi: 10.1007/s00134-020-05991-x.

[7] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; pii: S0140-6736(20)30566-3. doi: 10.1016/S0140-6736(20)30566-3.

[8] Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020; doi: 10.1001/jamainternmed.2020.0994.

[9] Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2020.

[10] American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 2018;41(5):917–928

[11] Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19 [published online ahead of print, 2020 Mar 31]. Diabetes Metab Res Rev. 2020

[12] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA (In press)

[13] Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 17: 181–192, 2019.

[14] Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426: 450–454, 2003.

[15] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell (In press)

[16] Cariou, B., Hadjadj, S., Wargny, M. et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 63, 1500–1515 (2020).

[17] Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JC. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 23: 623–628, 2006.

[18] Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318(5):E736-E741.

[19] Ferlita S, Yegiazaryan A, Noori N, et al. Type 2 Diabetes Mellitus and Altered Immune System Leading to Susceptibility to Pathogens, Especially Mycobacterium tuberculosis. J Clin Med. 2019;8(12):2219.

[20] Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. Diabetes Care. 2018

[21] Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47(3):193-199.

[22] Pinkney J. Prevention and cure of type 2 diabetes. BMJ 2002325232–233.

[23] Dixon AE, Peters U. The effect of obesity on lung function. Expert Rev Respir Med. 2018;12(9):755-767.

[24] Huttunen R, Syrjänen J. Obesity and the outcome of infection. Lancet Infect Dis. 2010;10(7):442-443.

[25] American Society of Hematology via Hematology.org/covid-19.

Dr. Cole is an Adjunct Professor and Director of Wound Care Research at Kent State University College of Podiatric Medicine. She also serves as Director of Wound Care Services for Cleveland Regency East Hospital and is the Medical Director at University Hospitals Ahuja Wound Care Center. She is board certified by the American Board of Podiatric Surgery. Her practice focus is on advanced wound care modalities and regenerative medicine. She has published on these topics and speaks nationally and internationally on limb preservation and wound care.