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Review Article

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COVID-19 and Diabetes

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Abstract

COVID-19 is a disease caused by a newly discovered coronavirus which is easily transmitted among humans. One of the reasons for the greater risk of diabetes is that insulin resistance promotes low-grade chronic inflammation, leaving the immune system weakened due to this constant state of alertness. Additional risk factors such as heart disease are often present in people infected with COVID-19 who have diabetes. It is important to point out that controlling blood sugar, before and during infection, can be helpful in fighting infection. Blood sugar control in people with diabetes is a procedure that can prevent certain infections and ensure a normal defense mechanism in response to infection.

The COVID-19 pandemic has caused concern around the world, especially in people with certain diseases such as diabetes. Data available to the American Heart Association show that among COVID-19 patients treated in intensive care units, 32 percent have diabetes, and among those hospitalized who are not in intensive care units, 24 percent have diabetes. It is estimated that diabetics have a nearly five times higher risk of death from COVID-19.

Keywords: COVID-19, Virus, Diabetes, Disease

Introduction

During the 20th century, health care delivery focused on the treatment of acute illness, often by solo practitioners in offices and hospitals [1]. In the 21st century, meeting the health needs and expectations of the population will require a focus on chronic rather than acute care. Chronic conditions are now the leading cause of illness, disability, and death in the United States, affecting almost half of the U.S. population and accounting for the majority of health care resources used. Indeed, chronic disease accounts for about 70 percent of all deaths in the United States. The major chronic disease killers are cardiovascular disease, cancer, diabetes, and chronic obstructive pulmonary disease. Although a greater proportion of the over-65 population has chronic conditions relative to other age groups, the majority of people with chronic conditions are under age 65.

The current coronavirus disease-2019 (COVID-19) pandemic presents a huge challenge for healthcare systems worldwide [2]. Many different risk factors are associated with disease severity, such as older age, diabetes, hypertension, and most recently obesity. The incidence of obesity has been on the rise for the past 25 years, reaching over 2 billion people throughout the world, and obesity itself could be considered a pandemic.

Patients with COVID-19 present primarily with fever, dry cough and fatigue or myalgia [3]. Although most patients with COVID-19 are thought to have a favorable prognosis, older patients and those with chronic diseases may have worse outcomes. Patients with chronic underlying conditions may develop viral pneumonia, dyspnea and hypoxemia within 1 week after onset of the disease, which may progress to respiratory or end-organ failure and even death.

The pathogenesis of COVID-19 is still not completely understood. Cytokine storm is thought to play an important role in disease severity. Neutrophilia was found in both the lung and peripheral blood of patients with SARS. The severity of lung damage correlated with higher numbers of neutrophils and macrophages in the peripheral blood and extensive pulmonary infiltration of these cells in patients with MERS. Neutrophils are the main source of cytokines and chemokines. The generation of cytokine storm can lead to acute respiratory distress syndrome, which is a leading cause of death in patients with SARS and MERS. This may explain the positive association between high fever and acute respiratory distress syndrome found at the early stages of COVID19 infection.

Diabetes

Diabetes once diagnosed is for life [4]. The perseverance and self discipline needed over a lifetime can often tax even the most robust of people to the limit. Those caring for them also require

perseverance and an understanding of humanity combined with a cautious optimism, to guide those with diabetes through the peaks and troughs of their lives.

Diabetes occurs either because of a lack of insulin or because of the presence of factors that oppose the action of insulin. The result of insufficient action of insulin is an increase in blood glucose concentration (hyperglycaemia). Many other metabolic abnormalities occur, notably an increase in ketone bodies in the blood when there is a severe lack of insulin. The diagnosis of diabetes must always be established by a blood glucose measurement made in an accredited laboratory.

The glucose tolerance test is not normally needed in routine clinical practice, and then only if uncertainty exists in younger patients, or to establish an exact diagnosis in pregnancy. For reliable results, glucose tolerance tests should be performed in the morning after an overnight fast, with the patient sitting quietly and not smoking; it is also important that the patient should have normal meals for the previous three days and should not have been dieting. False results may also occur if the patient has been ill recently or has had prolonged bed rest. Blood glucose concentrations are measured fasting and then one and two hours after a drink of 75 g of glucose in 250-350 ml water (in children 1•75 g/kg to a maximum of 75 g), preferably flavoured, for example, with pure lemon juice. Urine tests should be performed before the glucose drink and at one and two hours.

Type 1 diabetes (previously insulin dependent diabetes) is due to B-cell destruction, usually leading to absolute insulin deficiency. It can be immune mediated or idiopathic. Type 2 diabetes (previously non-insulin dependent diabetes) ranges from those with predominant insulin resistance associated with relative insulin deficiency, to those with a predominantly insulin secretory defect with insulin resistance.

The immune system plays a crucial role in the severity of COVID-19 and the development of pneumonia-induced acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [5]. Along with providing protection, both innate and T cell-based adaptive immune response dysregulate during severe SARS-CoV2 infection. This dysregulation is more pronounced in older population and patients with comorbidities (Diabetes, hypertension, obesity, other pulmonary and autoimmune diseases). However, COVID-19 patients develop protective antibodies (Abs) against SARS-CoV2, but they do not long for last. The induction of the immune response against the pathogen also requires metabolic energy that generates through the process of immunometabolism. The change in the metabolic stage of immune cells from homeostasis to an inflammatory or infectious environment is called immunometabolic reprogramming. The article describes the cellular immunology (macrophages, T cells, B cells, dendritic cells, NK cells and pulmonary epithelial cells (PEC) and vascular endothelial cells) and the associated immune response during COVID-19. Immunometabolism may serve as a cell-specific therapeutic approach to target COVID-19.

Generally, individuals with diabetes (type 1 or type 2) are at increased risk of respiratory tract infections relative to the healthy general population, which can be linked to hyperglycemia or non-optimal glycemic control [6]. Hyperglycemic state among individuals with diabetes could lead to impairment in cell-mediated immunity, phagocytosis, opsonization, and neutrophil chemotaxis and adherence to vascular endothelium. Both the presence of diabetes and a lack of glycemic control have been reported to be among the risk factors of severe illness and deaths in patients infected with novel coronaviruses, including the SARS-CoV-1 and Middle East Respiratory Syndrome (MERS)-CoV. A similar observation has been noticed among patients with SARS-CoV-2 infection, where a meta-analysis reported a significant association between the presence of diabetes and mortality, development of acute respiratory distress syndrome (ARDS), and disease progression in patients with COVID-19. In addition, a pooled analysis of observational studies involving patients with COVID-19 reported that those with diabetes had higher rates of being admitted to the intensive care unit compared to their counterparts without diabetes (37.0% versus 26.7%; $P = 0.028$). Nevertheless, it remains unclear if diabetes per se leads to increased susceptibility of or adversely affects the outcomes from novel coronavirus diseases including COVID-19, or if the associated cardiovascular and renal comorbidities among patients with diabetes are the underlying factors, or it is an interplay of the both. Indeed, both increased age and cardiovascular comorbidities [6] are associated with increased severity of COVID-19, and both are closely related to diabetes.

Coronavirus

Coronavirus are unsegmented single-stranded positive-strand RNA viruses [7]. They belong to the order Nidovirales, the family Coronaviridae, and the subfamily Orthocoronavirinae, which is divided into α, β, γ, and δ genera according to their serotypic and genomic characteristics. Coronaviruses belong to the genus Coronavirus of the family Coronaviridae. It is named after the wreath-shaped protrusions on the envelope of the virus.

Coronaviruses have an envelope encasing the RNA genome, and the virions (the whole viruses) are round or oval, often polymorphic, with a diameter of 50 to 200 nm. The novel coronavirus is 60 to 140 nm in diameter. The spike protein is located on the surface of the virus and forms a rodlike structure. As one of the main antigenic proteins of the virus, the spike protein is the main structure used for typing. The nucleocapsid protein encapsulates the viral genome and can be used as a diagnostic antigen.

Viruses generally can survive for several hours on smooth surfaces. If the temperature and humidity permit, they can survive for several days. The novel coronavirus is sensitive to ultraviolet rays and heat. Sustained heat at 132.8ºF for 30 minutes, ether, 75% alcohol, chlorinecontaining disinfectants, peracetic acid, chloroform, and other lipid solvents can effectively inactivate the virus. Chlorhexidine (also known as chlorhexidine gluconate) also effectively inactivates the virus.

In the context of viruses, once these chains of DNA or RNA are released into the cell they can behave in a number of ways [8]. They may do nothing at all. They may kill the cell, having forced its machinery to make copies of itself. They may remain in the cell but redirect that same machinery to their own reproductive

ends without killing it. In the case of some common viral diseases – chicken pox, measles – the virus may reactivate months or even decades later. Some viruses may so disrupt the reproductive machinery of the cell that they cause cancer. However, some may also become latent and incorporate permanently into the genes of the host. In the case of some viruses this incorporation may be harmless, or even beneficial, and as we have said, it can be passed from mother to offspring. These properties of viruses explain much of their capacity to cause epidemics. Their similarity to us, and the fact that we are partly composed of material indistinguishable from viruses, makes us sitting ducks for viral assault.

The freedom from the need to fuel and monitor their own reproduction allows viruses one much more crucial property. It permits a much greater capacity for mutation. Higher organisms that reproduce for themselves need to ensure faithful copying of their blueprint into the next generation. Defective cells will not function properly, and the animal may die as a consequence. They – we – therefore rely on a 'proof-reading' mechanism. The chances of a mutational error creeping in when your and my cells reproduce is lower than the order of one in a billion. Viruses are far sloppier. So long as they can enter a cell and reproduce they are 'happy'. A single virus may produce many thousands of offspring in a single cell.

Since December 2019, Wuhan City, Hubei Province has successively discovered multiple cases of patients with pneumonia infected by a novel type of coronavirus [9]. With the spread of the epidemic, other cases in China and abroad have also been found.

The new coronavirus belongs to the beta-type coronavirus. Its genetic characteristics are significantly different from SARSr-CoV and MERSr-CoV. Recently, the International Virus Classification Commission had proposal named the novel coronavirus as "SARS-CoV-2", and the World Health Organization has officially named the novel coronavirus pneumonia as "COVID-19."

At present, it has been confirmed that receptor-binding mechanism in infection of host cells by novel coronavirus is the binding of the coronavirus S protein to the human angiotensinconverting enzyme 2 (ACE2) protein, which involves in the regulation of blood pressure in the human body. It is widely present in the lungs, heart, kidneys, and intestines.

Coronavirus infections are proven to have a huge effect on the management of diabetes mellitus because they aggravate inflammation and alter immune system responses, leading to difficulties in glycaemic control [10]. SARS-CoV-2 infection also increases the risk of thromboembolism and is more likely to induce cardiorespiratory failure in patients with diabetes mellitus than in patients without diabetes mellitus. All of these mechanisms are now believed to contribute to the poor prognosis of patients with diabetes mellitus and COVID-19. During the COVID-19 pandemic, tight glycaemic control and management of cardiovascular risk factors are crucial for patients with diabetes mellitus. Medications used for both diabetes mellitus and CVD should be adjusted accordingly for people at high risk of SARS-CoV-2 infection.

Disease

The COVID-19 is a novel disease, which is under intensive investigation, in hope of contributing to the development of diagnosis and treatments [11]. The disease is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which was previously named as novel coronavirus (2019-nCoV). It is a new strain of zoonotic virus within the Coronaviridae family. Previous report showed the SARS-CoV-2 virus targets the epithelial cells that line the respiratory and digestive tracts. The virus infects these cells through binding onto angiotensin-converting enzyme 2 (ACE2) receptors that are expressed on these cell surfaces. The virus is highly infectious and transmits through close contact with symptomatically or asymptomatically infected individuals or aerosols. From the literature reports, the virus is noted to be highly contagious and fast spreading. The incubation period ranges from 0 to 14 days, with an average of 4–6 days before symptoms onset.

Severe cases of COVID-19 pneumonia can lead to multiple organ failure and even death. Recent literatures have postulated that COVID-19 pneumonia is likely to turn into a chronic disease similar as a flu, until effective vaccines or therapeutic treatments are available. In the light of possible long-term coexistence with humans globally, current priority includes developing methods in identifying and evaluating infected individuals.

Several intertwined pathways of interaction have been suggested to explain the relationship between diabetes and COVID-19 [12]. One possibility is that SARS-CoV-2 triggers higher stress levels, causing greater release of hyperglycemic hormones (e.g., glucocorticoids) leading to increased blood glucose levels. Approximately 10% of patients with diabetes and COVID-19 suffered at least one episode of hypoglycemia. The link between diabetes and atherosclerotic cardiovascular disease is well established, and hypoglycemia is known to both mobilize pro-inflammatory cells and increase platelet reactivity, contributing to heartrelated mortality in patients with diabetes. This suggests that people with diabetes and COVID-19 "are more susceptible to an inflammatory cytokine storm eventually leading to ARDS [Acute respiratory distress syndrome], shock, and rapid deterioration of COVID-19". Moreover, diabetes is associated with reduced expression of angiotensin-converting enzyme 2 (ACE2). This enzyme is a critical component of the biochemical pathway that regulates blood pressure and wound healing; in the lungs, it plays potent anti-inflammatory and anti-oxidant roles. The lowered ACE2 expression in diabetes might help explain the increased incidence of severe lung injury and ARDS with COVID-19. In addition, COVID-19 binds with and enters cells for RNA replication through ACE2 receptors on the surfaces of target cells. Once entry occurs, the host cell responds by sending out an enzyme that shears all the remaining ACE2 receptors off its surface, thereby eliminating molecules needed to maintain functioning lungs, heart, and other organs.

The body's anti-inflammatory process may compose the underlying mechanism that puts people with diabetes at risk for infection by affecting the body's response to pathogens. Research on the relationship between diabetes and infections shows that diabetes is associated with an increased incidence of infection,

most commonly of the skin, respiratory system, and blood. Poorly controlled diabetes has been linked to impaired functioning of important immune system components. Further, high blood glucose levels may prevent a normal respiratory burst, the process by which immune cells kill invasive pathogens by releasing toxic oxidative chemicals.

DM

COVID-19 is a novel and previously unrecognized virus and therefore lacks any associated herd immunity within the global human population [13]. This is important as herd immunity directly affects infectivity within any given population. With a complete lack of herd immunity (or history of any vaccination program), a pathogen has the potential to spread unimpeded within populations, like wildfire. It is helpful here to make a comparison with Seasonal Influenza (SI). Every year, millions of people globally are infected with SI, but this accounts for only a relatively low proportion of the global population (between 5% and 15%) due to a combination of herd immunity and vaccination for SI across the world.

These three factors, viral novelty, high infectivity, and global mobility, have created a perfect storm for the spread of COVID-19 around the world. The resultant global pandemic has become manifest over an alarmingly short timeframe, that seems to have taken everyone by surprise. The analogy with wildfire is apt. This wildfire, however is not one confined to one region or even one country, but one that affects the whole planet.

DM is a highly prevalent condition, with a rapid increase in the numbers affected over recent decades. Currently the global prevalence of DM exceeds 382 million. Furthermore, DM is a major cause of premature mortality, primarily from cardiovascular disease. Indeed, between 1990 and 2010, there was a doubling in the absolute number of deaths attributed to DM. Given the global prevalence of DM, and its broad implications for morbidity, mortality, overall wellbeing, and the global health-care economy, it is important to provide special attention to COVID-19 infection in the context of the patient with DM during this uncertain and unprecedented period.

We are still in the early stages of this global pandemic. There remain many unanswered questions particularly regarding optimal management of COVID-19 in the context of co-morbidities such as DM. Increased clarity will emerge over time in what is a rapidly developing and dynamic field.

In addition to hyperglycemia, DM also associates with chronic inflammation. Furthermore, type 2 diabetes mellitus (T2D) also associates with obesity and metabolic syndrome. Indeed, obesity per se increases the risk of severe SI. Therefore, some of the association of T2D with severe SI probably mediates through obesity-related effects.

Risk of infections (including respiratory infections) in DM (and obesity) may stem from the association of DM with deficiencies in immune functioning and immune surveillance that include cellular and humoral innate immunity. Such deficits in immune functioning may have contributed toward adverse outcomes and increased mortality from SI in patients with DM. There is compelling evidence to support the association of DM with a defective immune response to infections. DM is known to associate with a lower production of interferon (IFN)-α from dendritic cells, and diminished defense capacity from antibodies, and monocyte malfunction. A lower Cluster of Differentiation 4 (CD4) cell count in patients with DM may contribute toward a dysfunctional neutrophil response to infection and a diminished response to cytokines.

The interaction between Covid-19 and diabetes could be bi-directional, with Severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) potentially worsening pre-existing diabetes or even predisposing to diabetes in non-diabetic subjects [14]. Fasting glycemia and acute-onset diabetes has been reported among patients with SARS coronavirus (SARS-CoV or SARS-CoV-1) pneumonia. SARS coronavirus receptor, angiotensin-converting enzyme 2 (ACE2) are present in different human tissues like bronchus, lung parenchyma, ileum, testis, and cardiovascular, renal and gastrointestinal tissues, and pancreas. The organ involvements of SARS correlated with organ expression of ACE2. The localization of ACE2 expression in the endocrine part of the pancreas suggests that SARS coronavirus enters islets using ACE2 as its receptor and damages islets causing acute diabetes.

Diabetes and hypertension are the commonest comorbidities to COVID 19 [15]. Both diseases are very often cured with inhibitors of the angiotensin converting enzymes (ACE). COVID-19 remains bound to target cells by an angiotensin-converting enzyme 2 (ACE2), which is expressed in the epithelial cells of the lungs, blood vessels and intestine.

The expression of ACE2 is increased in patients treated with ACE and angiotensin II receptor blockers. Thus, it has been proposed that ACE2 expression could be elevated in these two classes of patients with hypertension and diabetes, which may promote COVID-19 infection and raise the likelihood of severe disease and number of fatalities.

Lack of control of glycaemia is a risk factor for severe conditions and negative outcomes. Nevertheless, the opposite is also true too and the risk of infection, including bacterial pneumonia, can be significantly lowered by good glycaemic control. The concern is that infections lead to the loss of glycaemic control, so diagnosis of hyperglycaemia in patients with respiratory issues becomes complicated during intercurrent fever disease, inadequate food consumption, so usage of medications such as glucocorticoids. To retain maximum glycaemic regulation, it is needed more regular monitoring of blood glucose and consistent improvement in antidiabetic care after the determined glucose levels.
A multidisciplinary team is required to treat patients with Covid-19 as well as monitoring as outpatients such as outpatients and the severe patients [16]. Especially the obese patient with metabolic syndrome has a disbalance as he has adiponectin and leptin are elevated. In diabetics, there is a decrease in the number of T cells regulating pro-inflammatory cytokines. Adipose tissue is resistant to T lymphocytes and promotes pro-inflammatory cytokines.

All of this promotes death of pancreatic cells with decreased insulin release and glucose deregulation. Diabetes patients have an

increased risk of infectious diseases. Steroids are diabetogenic and decrease immunity. It is important that the diabetic patient monitor glycemia either with monitoring or with telemedicine. Medicines such as next-generation empagliflozin can increase ketosis and the risk of vaginal infections. Hydration of the diabetic patient is very important.

Medical-based evidence has suggested that the risk of infectious diseases in the diabetic has weak evidence. This association with isolated observations promotes the existing possibility that glycemia could be an important factor in patients with Covid.

Conclusion

COVID-19 is a contagious disease caused by the newly discovered coronavirus. Most people with coronavirus disease have mild to moderate symptoms. The virus that causes COVID-19 is most often transmitted through droplets that occur when an infected person coughs, sneezes or exhales. These droplets are too heavy to fly through the air and fall quickly to the floor and other surfaces. A person can become infected by touching his eyes, nose or mouth after touching such contaminated surfaces or by inhaling the virus if he or she is in close to a person who has COVID-19. The situation is different for people with diabetes because they are at increased risk of COVID-19 infection due to their health condition.

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