Review Article

COVID-19 and Diabetes: Acknowledging the Bidirectional Link

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Abstract:

COVID-19 and diabetes mellitus have a dynamic and bidirectional relationship. Diabetes is a risk factor for COVID-19. Diabetes mellitus is linked to hypercoagulability, inflammation, hyperglycemia, and other conditions (obesity, hypertension, cardiovascular disease, chronic kidney disease). Hyperglycemia may worsen SARS-CoV-2 infection. As a result of direct pancreatic damage caused by COVID-19, the stress response is triggered response to infection (including cytokine storm), including the use of hyperglycemic prescription medications such as corticosteroids for severe COVID-19, new-onset hyperglycemia and diabetes have been linked to the virus, as well as rapidly deteriorating blood glucose control in pre-existing diabetes. Insulin resistance and decreased β-cell secretion cause hyperglycemia. Challenges still remain in establishing the connection between COVID-19 and diabetes, whilst the pandemic progresses.

Key words: COVID-19, Diabetes mellitus, Hyperglycemia, SARS-CoV-2, Cytokine storm.

Introduction:

SARS-CoV-2 (severe acute respiratory syndrome coronavirus2), which causes coronavirus disease (COVID-19), was discovered in Wuhan in December of 2019 and is now the greatest threat to global public health. COVID-19 was officially declared a pandemic by the World Health Organization on March 11th, 2020[1]. SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which causes coronavirus disease (COVID-19), was discovered in Wuhan in December of 2019 and is now the greatest threat to global public health. COVID-19 was officially declared a pandemic by the World Health Organization on March 11th, 2020[2]. Case-fatality ratios (CFRs) for patients with heart disease(10.5%), diabetes (7.3%), and hypertension (6%), were found to be higher in those with these conditions than in the general population (2.3%)[3].

It is a medical condition known as diabetes mellitus that is both chronic and noncommunicable. Insulin deficiency is the primary cause of glucose dysregulation in diabetes mellitus. Type 1 diabetes and type 2 diabetes are the two most common forms of diabetes. Patients with Type 1 diabetes lose their insulin-producing beta cells, whereas those with Type 2 diabetes develop insulin resistance and a depletion of their pancreatic beta cells[4]. As many as 463 million people worldwide are infected with this disease; the prevalence rate is 9.3%[5]. Long-term health issues such as cardiovascular disease and hypertension, obesity, as well as vasculopathy and a proinflammatory state accompanying it[6-7]. There is a chance that negative outcomes will be more common if COVID-19 affects a large number of people.

COVID-19 diagnosis, treatment, and epidemiology are bidirectionally linked. Our goal is to educate the public

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about the link between diabetes pathophysiology and COVID-19 and to offer recommendations. Future information may change these conclusions.

Immunological reactions to SARS-CoV-2 infection

SARS-CoV-2 virus can infect cells more easily because it has S1 and S2 subunits of spike protein in its spike protein complex (S). The S1 subunit contains NTDs and receptor-binding domains (RBD). A membrane-fusion between RBD of S1 subunit and ACE2 is facilitated by the S2 subunit so that viral RNA can enter host cells more easily[8]. Epitope that induces an immune response A strong antibody response is elicited by RBD, which aids in virus-cell attachment and virus attachment[9]. ECD (ectodomain) of S1 protein also contributes to antibody production; however, this contribution is distinct from that of the RBD and NP proteins[10]. Between 12 and 15 days after the onset of symptoms, virus-specific immunoglobulin G (IgG) seroconversion was observed, with nearly 100% seroconversion occurring between the ages of 19 and 22 days (POS). They go through a POS cycle of peak, plateau, and persistence at the lower level for a period of three weeks to three months from peak to persistence. A period of 2 to 8 weeks POS separates the peak and trough of IgM seroconversion, which takes place between 4 and 14 days[11].

There have been numerous seroprevalence and antibody kinetics studies for COVID-19 conducted around the world. In spite of this, the results of these studies have been highly inconclusive. Different countries and regions have different customs and laws. There are a number of factors that contribute to a person's prognosis, including socioeconomic, demographic, professional, and other variables[12]. Goldblatt et al. conducted a sero-survey among pediatric health care workers (HCW) from eight countries. It was only Cape Town, South Africa (10.36%) and Romania that had lower seroprevalence rates than London (16.93%). As expected, this result matched the country's COVID-19 death toll[13]. Another study conducted across ten locations in the United States found no connection between the seroprevalence of the San Francisco Bay Area (1%) and that of New York City (6.9%)[14]. As a result of the challenging serological surveillance of COVID-19, which is plagued by an immunological landscape resulting from the mixing of populations exposed to multiple strains of the virus over time and from worldwide vaccination campaigns, it is imperative that we gain a thorough understanding of the humoral responses to the virus, their durability, and their impact on the virus in order to devise an effective strategy for its control[15].

Immunopathology of COVID 19

The underlying immunopathogenesis of COVID 19 is a complex and multifaceted situation. The innate and adaptive immune system components both play a role in this scenario. Host endosomal pattern recognition receptors (PRRs), such as TLRs, NODs, RIG-1s, and RLRs, all recognize pathogen-associated molecular patterns (PAMPs) and activate downstream signaling pathways that activate transcription factors, such as nuclear factor-kappa (NF-$\kappa\beta$) and interferon regulatory factor) (IRFs)[16]. The production of type I interferons (IFNs) and pro-inflammatory cytokines ultimately aids in the removal of viruses from the body.

SARS CoV 2 infection inhibits anti-IFN I signaling via several viral proteins, including ORF6 and ORF3b, but not the NF-$\kappa\beta$ pathway[17]. A cytokine storm, or a burst of proinflammatory cytokines, occurs when viral replication is unchecked along with the recruitment of monocytes and macrophages. It's been discovered that the levels of several cytokines and chemokines, such as IFN-γ, IL-6 and MCP-1, GM-CSF and IL-1, are altered in patients with severe COVID-19[18]. As a result of a positive feedback loop in the immune system, an increase in inflammatory cytokines and toxic substances, such as ROS, can lead to multiple organ failure and even death[19].

It has been shown by both Magro et al. and Gao et al. that deviated activation of C5 in COVID-19 cases worsened the inflammatory lung injury caused by complement system-mediated microvascular injury and necrosis[20]. Lympopenia was always present in those with more severe COVID symptoms, even in those with adequate TH1 and CD8+ T-cell immune responses. Due to a decrease in CD4+ and CD8+ T-cells in the peripheral circulation, adaptive immune responses are compromised[21]. One method scientistis using to investigate the lymphoma in COVID 19 is the direct infection of T cells and macrophages with SARS-CoV2, while another method involves the depletion and exhaustion of T cells via cytokine-mediated means in COVID-19[22]. The spleen and lymph nodes can also be destroyed by the virus. With lymphopenia, COVID-19 patients are more vulnerable to bacterial infections[23]. When the same vicious cycle of cytokine storming attracts neutrophils and monocytes to the site of infection, ARDS, respiratory failure, shock, organ failure, and death are all possible outcomes[24].

Interrelationship between COVID-19 and Diabetes

Preexisting conditions such as diabetes, cancer, cardiovascular disease, hypertension, and acute kidney damage increase the risk of death from COVID-19[25-26].

Type 2 Diabetes is the most common comorbid condition of COVID-19. Study results have already shown that patients with severe and ICU-admitted COVID-19 cases have Type 2 Diabetes as a co-morbidity, which patients with moderate symptoms are a greater proportion of than those who have mild COVID-19 symptoms[27]. The body's ability to regulate viremia and inflammation is negatively impacted by hyperglycemia, which increases the risk of death and morbidity for patients[28].

Many viruses, such as the 2009 pandemic influenza A (H1N1)[29], SARS-CoV[30], and MERS-CoV[31], have been linked to diabetes and uncontrolled glycemia. The current SARS-CoV-2 pandemic has not shown any conclusive evidence that diabetes is linked to severe disease, according to various studies[32]. More recent studies from China[3] and Italy[33] found that the severity and mortality of COVID-19 were both increased in older patients with chronic diseases like diabetes and hypertension. In patients with COVID-19, glucose metabolism and the development of acute diabetic complications are poorly understood (e.g., ketoacidosis). In diabetics infected with SARS-CoV-2, hormones such as glucocorticoids and catecholamines may be released, resulting in elevated blood glucose levels and abnormal glucose variability[34]. According to a Wuhan retrospective study, 10% of T2DM patients who took COVID-19 had at least one episode of hypoglycemia (<3.9 mmol/L)[35]. As a result of an increase in diabetic mortality due to increased cardiovascular mortality, hypoglycemia has been shown to mobilize pro-inflammatory monocytes and increase platelet reactivity[36]. Hyper or hypoglycemia may alter SARS-CoV-2 virulence, or the virus may interfere with insulin secretion or glycemic regulation. The inflammatory and immunological response in these patients is still a mystery. No mention is made of COVID-19's glucose management options or the impact of standard diabetic medications on COVID-19 results.

COVID-19 and diabetes can both cause thrombocytopenia and leukopenia, though the latter is less common. Furthermore, IL-6, C-reactive protein, and D-dimer concentrations were all linked to disease severity[37].

More than twice as many SARS-CoV patients without prior diabetes who didn't receive steroids developed diabetes during their hospitalization, according to Chinese researchers, of 39 patients who didn't previously have diabetes. ACE2 immunostaining in the pancreas suggests that SARS-CoV may have caused insulin-dependent diabetes mellitus by destroying pancreatic islets[38]. COVID-19 patients may have pancreatic damage, which could lead to worse outcomes in diabetic patients, even if more evidence is needed. CoV-2 infection may not be more dangerous for diabetics because COVID-19 patients who had diabetes had a lower survival rate. Diabetic rates among those who are HIV-infected are comparable to those in the general population, and may even be lower than that. In 12 studies involving 2,108 Chinese people with COVID-19, a diabetes incidence rate of 10.3% was discovered[39], which was comparable to the national rate of 10.9% published in 2013[40]. The same results were found in a study involving 146 patients in Italy. There was an 8.9 percent (mean 65.3) prevalence of diabetes among these patients in 2018, compared to 11.0 percent (mean 65) among individuals aged 55-75 years from the same region[41]. Under reporting is a potential concern. The major receptor of MERS-CoV is dipeptidyl peptidase-4 (DPP-4)[42]. Because of its widespread use in the treatment of diabetes, more research is needed to determine whether or not DPP-4 acts as a receptor for SARS-CoV-2[43]. Antiviral medications such as Remdesi, Lopinavir, Ritonavir, Tocilizumab, Riboflavin and Interferon may be used to treat HIV. The safety and efficacy of COVID-19 treatments are being evaluated in clinical trials[44]. Diabetes patients can benefit from chloroquine and hydroxychloroquine. Chloroquine, a malaria and autoimmune disease treatment drug that may have broad antiviral activity, has been proposed.

Yang et al. in Guangzhou, China, in 2003 found that SARS patients with high plasma glucose levels and diabetes were independent predictors of mortality and morbidity, and metabolic control may improve their outcome. Diabetes has been used in numerous studies to predict the prognosis and course of COVID-19. Diabetes has also been linked to a higher risk of death in the COVID-19 study, according to several other studies[45]. Angiotensin-converting enzymes convert angiotensin I to angiotensin II, resulting in an increase in reactive oxygen species and oxidative stress (ACE). Hypertension, insulin resistance and endothelial dysfunction are all symptomatic of elevated levels of angiotensin II in the bloodstream. Due to the decrease in angiotensin II levels induced by ARB and ACEI, the already low cytosolic pH becomes even more conducive to viral infection.

Statins, diuretics, and inhibitors of the mineral corticoid system are among the medications prescribed to diabetics, in addition to pioglitazone. The efficacy of these drugs decreases with an increase in ACE2 concentrations. This combination of ACEIs, ARBs, and these medications could lead to an elevated ACE2 level during the outbreak of COVID-19. In diabetic patients with a low cytosolic pH, the viral load increases and the illness worsens. Patients with type 2 diabetes who take ACEIs and ARBs may experience an increased risk of death and illness[46].

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