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Covid and Diabetes: The Bilingual Relationship

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Abstract

The interrelationship between COVID-19 and diabetes is a critical area of study, given their bidirectional influence on disease severity and outcomes. COVID-19, caused by SARS-CoV-2, has led to significant global morbidity and mortality, particularly affecting individuals with preexisting conditions such as diabetes mellitus. Patients with diabetes are at an increased risk of severe COVID-19 complications, including acute respiratory distress syndrome, hyperglycemia, and inflammatory dysregulation. Additionally, SARS-CoV-2 may exacerbate metabolic disturbances, potentially leading to new-onset diabetes. This article explores the pathophysiological mechanisms underlying the COVID-19-diabetes nexus, including the role of angiotensin-converting enzyme 2 (ACE2) receptors, inflammatory responses, and glucose metabolism dysregulation. Furthermore, we discuss the therapeutic challenges posed by COVID-19 in diabetic patients, including the impact of common antidiabetic and antiviral treatments. The potential role of bioactive compounds such as quercetin, kaempferol, and curcumin in mitigating disease progression is also examined. Understanding the intricate relationship between these conditions is crucial for developing targeted interventions and improving patient outcomes.

Keywords: COVID-19; Diabetes Mellitus; SARS-CoV-2; Hyperglycemia; ACE2 Receptors; Inflammatory Response; Metabolic Dysregulation; Diabetes Comorbidities

Introduction

Severe acute respiratory syndrome corona-virus 2 (SARS-CoV-2), the novel coronavirus which causes COVID-19, was first reported into Wuhan, China, around December 2019. As of 15th August 2022, India has 44,268,381 reported cases of COVID-19 with 527,069 deaths (https://covid19.who.int/region/searo/country/in). Globally, there are 588,331,997 positive cases about COVID-19 in 198 Countries, which resulting in 6,432,704 deaths as per the report of World Health Organization (https://covid19.who.int/). The WHO declared the virus as a global epidemic on March 11, 2021 expressing situation over the alarming occurrence or prevalence regarding the disease.

The burden of diabetes is high and increasing worldwide, and in developing countries such as India, particularly fueled by the growing rate of unhealthy lifestyles [1]. Around 463 million people worldwide was diabetic in 2020 whereas 88 million people of them only from the Southeast Asian region alone. Of these 88 million people, 77 million were Indians. This diabetic count is expected to rise over 134 million by 2045 (Ref). About 57% of these people are still undiagnosed. According to the World Health Organization (WHO), non-communicable diseases (NCDs) accounted for 74% of deaths worldwide by 2019, of which diabetes has killed 1.6 million people, making it the ninth leading cause of death worldwide (http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death). By the year 2035, around 592 million people might die because of diabetes as predicted [2]. Diabetes has reached epidemic proportions in many developing economies, such as China and India. According to the WHO, the incidence of diabetes is growing rapidly in low- and middle-income countries. Rapid socio-economic changes along with urban and industrial growth are the leading causes of diabetes in the world, with other risk factors associated with population growth, unhealthy eating habits, and sedentary health also play an important role [3].

There is a two-way relationship between Covid-19 and diabetes. At one hand, diabetes is associated with an increased risk of severe Covid-19. Early diabetes and severe metabolic complications of pre-existing diabetes, including diabetic ketoacidosis and hyperosmolarity where high insulin levels are noted, have been seen in patients with Covid-19. This manifestation of diabetes poses challenges to clinical management and raises the complex pathophysiology of Covid-19-related diabetes [4]. Patients with diabetes, especially those with COVID-19, are at risk of developing serious illnesses. In a study of 1000 COVID-19 patients, diabetes was present in 16.2% of patients with severe illness, The end result for these patients was mechanical ventilation and / or death. This shows a fourfold increase in COVID-19 mortality among patients with diabetes or hyperglycemia. In a retrospective study of 72,314 COVID-19 patients, the mortality rate (7.3%) was significantly higher in patients with diabetes.

Severe acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the Covid-19 virus, binds to angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in vital metabolic organs and tissues, including pancreatic beta cells, adipose tissues, small intestines, and kidneys. Therefore, it appears that SARS-CoV-2 may cause a pleiotropic modification of glucose metabolism that may complicate the pathophysiology of existing diabetes or lead to new mechanism of the disease [3].

Glucose-lowering drugs commonly used in the treatment of diabetes may contribute to COVID-19 pathogenesis, and these effects may influence the treatment of diabetic patients and COVID-19. (The most promising treatment is remdesivir. Remdesivir has potent in vitro activity against SARS-CoV-2. A few drugs, such as Rivatirin, interferon (IFN), favipiravir (FPV), and lopinavir (LPV) / ritonavir (RTV), have been used in patients with SARS or MERS. Arbidol Inhibits viral cell membrane binding by membrane lipids. Drugs that inhibit viral RNA replication include lopinavir / ritonavir and darunavir. The use of lopinavir / ritonavir (LPVr) in severe acute respiratory syndrome (SARS) has shown a positive clinical response, but in the SARS-CoV-2 infection, it shows limited efficacy. Emdesivir shortens the duration of COVID-19 but does not affect mortality. Favipiravir inhibits the activity of RNA polymerase, but this drug is currently being tested in the treatment of COVID-19. Also, the use of an classical anticoagulant treatment such as heparin was first used in COVID-19 patients at risk for thrombotic and thromboembolic events.

There are a good number of secondary metabolites, especially high-dose flavonoids, which are given antibacterial or other beneficial health functions such as immune rejuvenation or anti-inflammatory action that may play a role in preventing or alleviating viral infections and / or preventing the development of SARS induced novels. coronavirus. Recently, Solnier et al. promote quercetin as an effective plant bio active for SARS-CoV-2. In fact, several flavanols have shown antiviral activity against coronaviruses (such as SARS-Cov and MERS-CoV) by inhibiting 3CL and PL pro proteases. Anther important flavanol is kaempferol, the second major metabolite found in a variety of edible plants. The highest dose of this compound is found in capers and saffron (259 and 205 mg / 100 g, respectively). The glycoside form of kaempferol is astragalin, which is well known for its many therapeutic properties such as antioxidant, anti-inflammatory and antiviral. Curcumin, a phenolic compound present in the roots of Curcuma longa is another popular phytochemical because it has been tested as a SARS-CoV-2 inhibitors. Among other phenolics exhibiting antiviral activity, phloretin should also be considered a Covid antidote because it is found everywhere in vegetables and fruits (among them, apples and pears) and epigallocatechin gallate (commonly found in green tea, onions, plum, apple skin) because, in addition to being given antimicrobial properties, it has the potential to reduce the risk of infections that appear to be part of chronic inflammation. Finally, sulforaphanes comprising sulforaphanes, distributed to cruciferous plants such as broccoli, may be particularly interesting antiviral shelters because their action depends on the action of transcription factors that change the cellular mechanisms responsible for antiviral effects. The effect of celastrol, a pentacyclic triterpenoid, may be a promising bioactive for the treatment of COVID-19 due to its ability to inhibit TMPRSS2 proteins and, thus, reduce S protein cracking and subsequent viral infiltration.

Pumpkin seeds have exhibited acute hypoglycaemic activity (blood sugar lowering). D-chiro-Inositol was identified in pumpkin (especially in *Cucurbita ficifolia*) and this compound has been considered as an insulin action mediator (insulin sensitiser). Phenolic phytochemicals of pumpkin have antidiabetic effects in terms of b-glucosidase and a-amylase inhibition. Furthermore, hypoglycaemic substances from pumpkin, isolated from protein-bound polysaccharide of the pumpkin fruits. When this protein-bound polysaccharide from pumpkin fruits (PBPP) was evaluated, it was found that PBPP can increase the levels of serum insulin, reduce the blood glucose levels and improve tolerance of glucose.

Quercetin has been shown to help reduce the severity of numbness, movement pain, and irritability in patients with type 2 neuropathy. Kaempferol may be a naturally occurring antidiabetic compound that protects the survival of pancreatic beta cells and acts in a hostile environment that could lead to type 2 diabetes. Curcumin slows down the development of diabetes improves beta-cell function, prevents beta-cell death, and reduces insulin resistance. Another bioactive compound is sulforaphane, which is found in broccoli and other vegetables. It has been shown that sulforaphane inhibits glucose production in enlarged cells and improves glucose tolerance in mice in a high-fat or high-fructose diet. Sulforaphane containing broccoli sprout extract was well tolerated and improved fasting glucose in obese human patients and dysregulated type 2 diabetes.

Discussion

Side effect: Remdesivir is not approved by the US Food and Drug Administration and is currently being tested in ongoing randomized trials. Oseltamivir has not been shown to be effective and corticosteroids are not currently recommended. Current clinical evidence does not support discontinuation of angiotensin converting enzyme inhibitors or angiotensin receptor blockers in patients with COVID-19. A severe COVID-19 infection and its treatment with steroids can have a specific adverse effect on diabetes itself and lead to worsening of hyperglycemia through increased insulin resistance and reduced β-cell secretary function. Worsening hyperglycemia, in turn, may adversely affect the course of COVID-19.

Diabetes - Covid Fatal Mechanism

Presence of diabetes mellitus and individual degree of hyperglycemia appear to be independently associated with COVID-19 severity and increased mortality. In addition, the presence of typical complications of diabetes mellitus (CVD, heart failure and chronic kidney disease) increas-

es COVID-19 mortality. Some pathophysiological mechanisms leading to increased cardiovascular and all-cause mortality after SARS-CoV-2 infection in patients with diabetes mellitus (T2DM). Infection with severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) can lead to increased blood pressure levels of inflammatory mediators in the blood, including lipopolysaccharide, inflammatory cytokines, and toxic metabolites. Modulation (increase or decrease) of natural killer cell activity and IFNγ production can increase interstitial and/or vascular permeability for proinflammatory products. In addition, infection with SARS-CoV-2 causes increased production of reactive oxygen species (ROS). These effects lead to lung fibrosis, acute lung injury and acute respiratory distress syndrome (ARDS).

Critically ill patients with COVID-19 admitted to intensive care units in the USA found the prevalence of diabetes mellitus 58% and 33%, suggesting a link between severe COVID-19 and diabetes mellitus. Various mechanisms are thought to be responsible for the apparent clinical severity of COVID-19 in persons with diabetes mellitus. In addition, drugs commonly used in the clinical care of COVID-19 patients, such as systemic corticosteroids or antiviral agents, may contribute to worsening of hyperglycemia. Darker red indicates highlighted processes in patients with type 2 diabetes (T2DM). Severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) infection causes tissue hypoxia by increasing metabolic rate, resulting in interstitial lung injury and acute respiratory distress syndrome. Patients with diabetes mellitus and coronavirus disease 2019 (COVID-19) exhibit dysregulation of glucose homeostasis, exacerbation of inflammation and impaired immune system function. These conditions increase oxidative stress, cytokine production, and endothelial dysfunction, resulting in an increased risk of thromboembolism and damage to vital organs. All these factors contribute to the increased severity of COVID-19 and rapid progression to cardiorespiratory failure in patients with diabetes mellitus.

Bio Actives in Relation with Covid 19 and Diabetic Comorbidity

Recently, Solnier et al. They suggested **quercetin** as a good SARS-CoV-2 candidate. In fact, several flavanols showed antiviral activity against coronaviruses (such as SARS-Cov and MERS-CoV) through inhibition of 3CL and PLpro proteases. Since old SARS-CoV and new SARS-CoV-2 show high sequence similarity in spike glycoproteins, flavanols can also be expected to inhibit entry of SARS-CoV-2 into host cells. Moreover, the spike protein of the novel virus binds to the ACE2 receptor with higher affinity compared to SARS-CoV. Therefore, inhibition of ACE2 through a competitive binding appears to be a good approach to prevent SARS-CoV-2 infections. In this context, quercetin exerts potent inhibitory effects on ACE2 in vitro as well as in vivo. Quercetin's antidiabetic qualities include stimulation of glucose uptake via a MAPK insulin-dependent mechanism. Stimulation of the mechanism in skeletal muscles resulted in the displacement of glucose transporter 4 (GLUT4). This role of MAPK differs from its role in the liver, where it decreases sugar production mostly through down-regulation of essential gluconeogenesis enzymes, type 2 diabetes neuropathy.

Kaempferol showed potent antiviral properties due to inhibition of protein kinase B (Akt) signaling. The potency of kaempferol in blocking a cation-selective channel expressed in the infected cell of SARS-CoV (3a channel) has been demonstrated. Kaempferol (20 μM) blocked more than 50% of these channels. In an in vivo study, kaempferol (15 mg/kg, eg) reduced pulmonary edema, lung wet/dry weight, myeloperoxidase activity, pulmonary capillary permeability, and inflammatory cell count in BALB/C mice intranasally infected with H9N2 influenza virus. Kaempferol also decreased TNF-α, IL-1β and IL-6 production and ROS activity and malondialdehyde production while increasing superoxide dismutase activity.

Kaempferol, a flavonol compound, has cytoprotective effects on cultured clonal beta cells and pancreatic human islets. Kaempferol treatment dose-dependently increased viability, inhibited cellular apoptosis, and decreased caspase-3 activity in beta cells and human islets chronically exposed to high glucose. Kaempferol may be a naturally occurring anti-diabetic compound by preserving pancreatic beta cell survival and function in a hostile environment that could otherwise lead to type 2 diabetes.

Curcumin has different pharmacological and

biological effects. The functional mechanism by which curcumin exerts its effect appears to be the modulation of many signaling molecules. Curcumin extract delays the development of diabetes, improves β cell functions, prevents β cell death and reduces insulin resistance. Curcumin is a natural phenolic compound found in turmeric (*Curcuma longa L.*), a plant native to India and Southeast Asia, where curcumin is used as a traditional medicine to treat a variety of disorders. In Europe, this molecule is used as a food dye due to its yellow color and is classified as a food additive. It is active against various human viruses, bacteria and fungi. Today, foods high in curcumin are considered as SARS-CoV-2 inhibitors. Despite its poor bioavailability, some nanoparticle-based approaches have been developed recently. It has also been shown that different compounds can increase the bioavailability of curcumin. It can increase the bioavailability of curcumin by up to 20 times, especially when combined with piperine, the main active ingredient in black pepper.

Sulforaphanes are not phenolic compounds, but have antiviral potential. They belong to the isothiocyanate group of nitrogen-containing plant secondary metabolites and are classified as sulfur compounds. Sulforaphanes are stored as their inactive form, glucoraphan. This natural compound is mainly found in cruciferous vegetables (such as broccoli), used to prevent and support chronic diseases, and is presumed to play a role in human aging. It has also been suggested that sulforaphane, like other natural phytochemicals, can be used in the treatment of SARS-CoV-2. Cruciferous plants can release glucoraphanin, which is converted by the plant to sulforaphane, which activates Nrf2, an important transcription factor that induces an antiviral effect and prevents oxidative stress. Nrf2 activity decreases with age, making the elderly more susceptible to oxidative stress-mediated diseases. It can reverse the disease signature. Sulforaphane suppressed glucose production from hepatic cells by nuclear translocation of nuclear factor erythroid 2-related factor 2 (NRF2) and reduced the expression of key enzymes in gluconeogenesis. Furthermore, sulforaphane reversed the disease signature in the livers of diabetic animals and attenuated the exaggerated glucose production and glucose intolerance with a magnitude similar to that of metformin. Finally, sulforaphane provided as a concentrated broccoli sprout extract reduced fasting blood sugar and glycosylated hemoglobin (HbA1c) in obese patients with irregular type 2 diabetes.

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