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RESEARCH ARTICLE

A REVIEW STUDY OF RELATIONSHIP BETWEEN COVID-19 AND HYPERGLYCAEMIA

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ABSTRACT

It has been reported that, hyperglycaemia is more common in patients with coronavirus disease 2019 (COVID-19). COVID-19, which triggered by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), can cause extrapulmonary symptoms such as diabetes mellitus (DM) and hyperglycaemia, which both indicate a poor prognosis and a higher chance of death.SARS-CoV-2 infects the pancreas through angiotensin-converting enzyme 2 (ACE2), which is abundantly expressed in the pancreas relative to other organs, causing pancreatic damage, insulin secretion impairment, and hyperglycemia in non-DM patients. Thus, the present study provides an overview of the potential association or relation or linkage between COVID-19 and hyperglycemia as a risk factor for the development of diabetes mellitus in relation to diabetes pharmacotherapy.

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INTRODUCTION

We are all well acquainted with the term hyperglycaemia. It is a condition with high blood glucose. Normally it is believed that it occurs when too much sugar in the blood. This develops usually due to lack of insulin or when body can't utilize insulin properly. But during the corona epidemic, it was commonly seen that hyperglycaemia developed easily in those people who had been suffering from corona infection. This type of hyperglycaemia was particularly more common in people who emerged after becoming serious covid infection or emerged after admitted in ICU. According to the study published in "Cell Metabolism" on Sept. 15, 2021.The researchers discovered that hyperglycaemia—high blood sugar level is widespread in hospitalised COVID-19 patients and is substantially related with poor outcomes. The term hyperglycaemia is linked with inflammation and weakened immunity against infections or decreased infection resistance and was identified as a substantial risk factor for severe COVID-19 early in the pandemic (Henderson E. 2021). Dr. Lo and colleagues studied the data of 3,854 patients who were hospitalised with COVID-19 at NewYork-PresbyterianLower Manhattan Hospital in the first few months of the epidemic in the United States to better understand this crucial yet puzzling element of COVID-19.They discovered that a shockingly high percentage of these individuals (49.7%) had hyperglycaemia or developed it during their hospital stays. Hyperglycaemia in these COVID-19 patients was also strikingly associated with worse outcomes. Patients with hyperglycaemia were 9 times more likely than those with normal blood sugar levels to have severe lung dysfunction (acute respiratory distress syndrome, or ARDS), 15 times more likely to require mechanical ventilation, and 3 times more likely to die. Surprisingly, the researchers discovered that hyperglycaemia and the dangerous hazards it carries also occur in other types of severe lung dysfunction that aren't caused by COVID-19.The study of Dr. Lo also says, obese people may be more sensitive to COVID-19 because they may already have some insulin resistance and fat cell malfunction, and their fat cells may be more prone to infection. Epidemiologic evidence says that type 2 diabetes mellitus (T2DM) is the second most common comorbidity of COVID-19,and patients with T2DM are more venerable to SARS-CoV-2 infection (Li *et al*., 2020; Muniyappa and Gubbi, 2020).According to a large body of evidence from around the world COVID-19 patients with hyperglycaemia or T2DM have a dramatically increased release of inflammatory cytokines, known as the cytokine storm syndrome, which leads to immunosuppression and multi-organ failure. (Ye, *et al*., 2020). Evidence from the COVID-19 pandemic suggests that hyperglycaemia may enhance the risk of mortality in COVID-19 patients(Bode *et al*., 2020).Indeed, high fasting blood glucose (7.0 mmol/L) or acute uncontrolled hyperglycaemia (defined as blood glucose >10 mmol/L twice in any 24-hour

period) are linked to COVID-19 morbidity and mortality(Yang *et al*., 2020). Furthermore, a recent study found that T2DM is linked to a greater death rate among 7300 COVID-19 individuals(Zhu *et al*., 2020).On the other hand, diabetic individuals with better control of blood glucose levels have a significantly lower fatality rate(Zhu *et al*., 2020).These data imply that hyperglycaemia in the early stages of COVID-19 may be a key factor in predicting prognostic severity(Apicella *et al*., 2020).People with diabetes are more susceptible to SARS-CoV-2 infection, and SARS-CoV-2 infection may raise blood glucose levels, implying that hyperglycaemia is a major element in the COVID-19-diabetes relationship. Insulin infusion has recently been demonstrated to be an effective strategy for reaching glycaemic objectives and enhancing COVID-19 clinical outcomes (Sardu *et al*., 2020). Piva *et al*. reported that COVID-19 patients admitted to ICUs frequently had underlying cardiovascular disease and diabetes. Hamming *et al*. suggested that the virus that causes Covid-19, coronavirus 2 (SARS-CoV-2), attaches to angiotensin-converting enzyme 2 (ACE2) receptors, which are found in critical metabolic organs and tissues such as pancreatic beta cells, adipose tissue, the small intestine, and the kidneys. As a result, it's possible that SARS-CoV-2 causes pleiotropic changes in glucose metabolism, which could exacerbate the pathophysiology of pre-existing diabetes or lead to new disease processes (Rubino *et al*.,2020). Other viruses that bind to ACE2 receptors have also been implicated as a viral aetiology of ketosis-prone diabetes (Yang *et al*., 2010).Patients with SARS coronavirus 1 pneumonia have been found to have higher rates of fasting glycaemia and acute-onset diabetes than those with non-SARS pneumonia (Yang *et al*., 2010).To address these concerns, a global registry of patients with Covid-19–related diabetes has been developed by an international collaboration of prominent diabetes experts collaborating in the CoviDIAB Project (covidiab .e-dendrite.com). According to centres for disease control; people with type 2 diabetes are now at a greater risk of serious disease from COVID-19, while people with type 1 diabetes or gestational diabetes may also be at risk. Despite our early discovery of the link between hyperglycaemia and dangerous consequences, the pathophysiological mechanisms behind hyperglycaemia in COVID-19 are still unknown (Accili, 2021; Lockhart and O'Rahilly, 2020).

MATERIALS AND METHODS

We established a protocol for a systematic review of the COVID-19 articles in order to examine the report of ethical considerations in these works. A systematic search of the PubMed, Sciencedirect, Cochrane, SCOPUS, and CINAHL databases was conducted. For this analysis, papers that reported on COVID-19 related with diabetes mellitus and hyperglycaemia, Clinical management of diabetes mellitus and COVID-19, Critical illness due to COVID19 and diabetes mellitus and paper with related topic were chosen. The following terms and keywords were used to collect data: [COVID-19], [SARSCoV-2], [Hyperglycaemia], [Diabetes Mellitus] and [Pancreatic injury].Language and genre of published publications, as well as pre-printed data, were not restricted.

STUDY: COVID-19 has been linked to hyperglycaemia, which is thought to be a direct predictor of a poor prognosis for the disease and an increased chance of death (Somasundaram *et al*., 2020).

Type of diabetes associated with covid-19: It is currently unknown that the COVID-19-related new-onset diabetes is type 1, type 2, or a complicated subtype of diabetes (Khunti *et al*.2021).Although insulin deficiency is normally caused by an autoimmune process in T1D (Type-1 diabetes), it could be caused by the loss of b- cells in SARS-CoV-2 infection. Unfortunately, there have only been a few case reports on islet cell antibodies in persons with new-onset diabetes.(Hollstein *et al*., 2020, Kichay *et al*., 2020). Multiple investigations have found a large number of cases of diabetes ketoacidosis (DKA) in persons with and without COVID-19, implying that SARS-CoV-2 has a direct effect on pancreatic b-cells (Khunti*et al*.2021). In a study of hospitalised patients with SARS-CoV-1 infection it has been observed that Angiotensin-converting enzyme 2 (ACE2) protein immunostaining was significant in pancreatic islets but poor in exocrine organs. Furthermore, long-term hyperglycemia may exacerbate COVID-19 by glycating pancreatic ACE2, which increases SARS-CoV-2 binding and entrance at pancreatic b-cells. According to many studies, aberrant expression of cell ACE2 receptors in various tissues lowers the protective effect against viral entry, hence exacerbating the severity and bad outcomes of SARS-CoV-2 infection (Kuraishy, 2020).

New onset of type 2 diabetes in COVID-19 Patients: Although the exact mechanisms underlying the development of new-onset diabetes in people with COVID-19 are unknown, it is likely that a number of complex, interrelated etiologies are involved, including impairments in both glucose disposal and insulin secretion, stress hyperglycemia, preadmission diabetes, and steroid-induced diabetes. Study of Al-kuraishy, 2020 state that COVID-19 causes cytokine storm (CS) and inflammation. Cytokine storm (CS) and inflammation cause profound elevations in the levels of interleukin (IL)-6 as well astumor necrosis factor alpha (TNF-alpha), which cause peripheral insulin resistance (IR). The high level of TNF-a and IL-6 in CS impair pancreatic beta-cell function and inhibit insulin secretion (Mehta, 2020).The role of SARS-CoV-2 in diabetes induction is likely to be more complicated than just pancreatic ACE2 expression and cell death (Drucker, 2021). New-onset diabetes, like many other clinical scenarios, can be caused by a variety of pathogenic processes involving variables that cause autoimmunity, cell stress, or insulin resistance in the liver, skeletal muscle, and adipose tissues. Furthermore, local hypoxia and inflammation caused by SARS-CoV-2 infection of the islet microvasculature could cause cells to be harmed indirectly (Atkinson and Powers, 2021).

Pancreatic injury and COVID-19: Pancreatic injury (PI) is often considered as acute pancreatitis; however acute pancreatitis is rarely reported in COVID-19 (Al-Nami *et al*., 2019). According to various researches, COVID-19-induced PI is diagnosed with a complete medical history, physical examination, and ultrasound imaging with an increase in serum lipase levels. Although, abdominal CT scan imaging is recommended in chronic cases (Alves *et al*., 2020). PI can arise in COVID-19 either directly through SARS-CoV-2 invasion or indirectly through the induction of CS (Wang *et al*., 2020). Study of Zhang *et al*. state that SARS-CoV was found in pancreatic tissue, implying that the virus binds to ACE2, which is abundantly expressed in pancreatic tissue, primarily in b-cells and exocrine ducts (Zhang *et al*.,

2003).According to recent research, SARS-CoV-2 affects pancreatic lipase as well as peripheral adipose tissue, causing PI and lipotoxicity, which contribute to CS induction (Taneera *et al*., 2020).Study of Gomes state that the post-mortem report of patients died due to SARS-CoV and SARS-CoV-2 had a higher proliferation of these viruses in the pancreatic tissues. As a result, SARS-CoV-2 could cause PI either directly or indirectly, with endocrine and exocrine dysfunctions manifesting as acute pancreatitis and transitory hyperglycemia.

Relation of anti-COVID-19 medicine with blood glucose level: Drugs which are used for treatment of COVID-19 may affect the blood glucose level of patients. These drugs may cause blood glucose variability in patients with diabetes mellitus as well as non-diabetes mellitus patients. Drugs like; Chloroquine and hydroxychloroquine show controlling effect on SARS-CoV-2 replication as well as modulating COVID-19-induced CS. This occurs due to the potent anti-inflammatory and immunomodulating effects of these drugs (Liu *et al*., 2020). From the investigation it has been found that the glycemic indices, b-cell function, and insulin secretion are all improved by the drug hydroxychloroquine, which can be effectively used to treat uncontrolled T2DM. Thus it can be assumed that hydroxychloroquine therapy in COVID-19 may lead to hypoglycemia since this drug reduces insulin degradation and improves insulin storage with augmentation of peripheral glucose metabolism (Wondafrash *et al*., 2020). Drugs like dexamethasone which is effective in COVID-19 patients, reducing the exaggerated immune response-induced ALI(acute lung injury) and ARDS (acute respiratory distress syndrome).Despite this benefit, dexamethasone inhibits viral clearance as well as immunological response (Hasan *et al*.,2020).Furthermore, even in non-DM patients, corticosteroid therapy is linked to hyperglycemia in COVID-19 individuals. It has been seen that the lower dose of methylprednisolone is ineffective in for management of COVID-19 patient and its higher dosage become effective in suppressing CS but the high dose of this may aggravate hyperglycemia in DM (Hasan *et al*., 2020 &Saad *et al*., 2020). To avoid hyperglycemia-related problems, COVID-19 patients who receive corticosteroids must have rigorous glucose monitoring.

CONCLUSION

Due to pre-existing comorbidities and a proinflammatory profile, SARS-CoV-2 infection in DM patients is more severe and linked with poor clinical outcomes. Due to the development of a cytokine storm (CS), down regulation of ACE2, and direct damage of pancreatic b-cells, SARS-CoV-2 infection affects glucose homeostasis and metabolism in DM and non-DM patients. As a result, the substantial anti-inflammatory impact of diabetic pharmacotherapies may help to reduce the severity of COVID-19.Furthermore, through altering the expression of ACE2 receptors; some anti-diabetic drugs can lower SARSCoV-2 infectivity and severity.

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