A comprehensive look into the association of diabetes with COVID- 19

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing my degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "A comprehensive look into the association of diabetes with COVID- 19" submitted by Sabrina Islam Antora (17146035) of spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on January 2022.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

This review aims to analyze the impact of diabetes on COVID-19 infection. Studies have shown a reciprocal relationship between diabetes and COVID-19. On one side, diabetes is associated with an increased risk of severe COVID-19 infection. On the flip side, patients with COVID-19 infection have been diagnosed with new-onset diabetes, serious metabolic complications of pre-existing diabetes where an exceptionally high dose of insulin was required. Diabetes is a disease that suppresses the immune system's functions. Diabetic patients' down-regulated immune responses have a major contribution to worsening aggravation and increasing mortality rate of COVID-19 infected patients. SARS-COV-2 causes pleiotropic alterations in glucose metabolism which in turn complicates the pathophysiology of pre-existing diabetes or direct to new mechanisms of diabetes. Due to the impaired immune response of diabetic patients' higher number of COVID-19 viruses enters the cell and facilitate severe infection. Hence, this group of patients requires careful clinical management.

Keywords: Diabetes, COVID-19, ICU, Insulin, Vaccine, Isolation.

Dedication

Dedicated to my parents

Acknowledgement

The first and foremost praises and thanks to Allah, Almighty for his shower of blessings throughout my research work to successfully complete my work. I would like to express my deep and sincere gratitude to my thesis supervisor Dr. Raushanara Akter, Associate Professor, Department of Pharmacy, Brac University. She has provided a great support to complete my project through her expert supervision and guidance through the project by sharing her valuable knowledge. Next, I want to acknowledge Dr. Eva Rahman Kabir, Chairperson, Department of Pharmacy, Brac University. I am very grateful to have her as my teacher and chairperson. I would like to thank Md. Kaykobad Hossain, Teaching Assistant, Department of pharmacy, BRAC University for his valuable support throughout my whole University journey. Last but not least I am thankful to both of my project group mates for being very helpful throughout the time.

Table of Contents

Declaration......ii

Approval iii

Ethics Statement......iv

Abstract......v

Dedication vi

Acknowledgement......vii

Table of Contents viii

List of Tables x

List of Figures......xi

List of Acronyms xii

Chapter 1 Introduction......1

1.1 Corona Virus and Its Types 3

1.2 Origin of COVID 19 3

1.3 Pathophysiology of SARS COV-2......4

1.4 Transmission of COVID 19 Worldwide 5

1.5 Sign and Symptoms and suspects 6

1.6 Diabetes and Its Types 7

1.7 Prevalence and Severity......8

1.8 Diabetes and COVID 19 Susceptibility 8

1.9 Rational of The Study 9

1.10 Aim and Objects of The Study....9

Chapter 2 Methodology....11

Chapter 3 Association of Diabetes with COVID 19....12

Chapter 4 Diabetes-Related Comorbidities....20

4.1 Mortality....20

Chapter 5 Diagnosis of COVID-19....22

Chapter 6 Treatment Options for COVID 19 Patient with Diabetes....24

6.1 Care for COVID 19 Patients Who Has Diabetes....28

6.2 Self-management....29

6.3 Diet....30

6.4 Physical activity....31

Chapter 7 Conclusion & Future Recommendation....33

References....34

List of Tables

Table 1: Complications Associated to COVID-19 patients with diabetes. 15

Table 2 : COVID-19 tests and testing facilities in SAARC countries as of May 10, 2020 22

Table 3: Treatment options for COVID-19 patients with diabetes. 25

Table 4: Choosing Anti-Diabetic Drugs During COVID-19 26

List of Figures

Figure 1: Pathophysiology of SARS CoV-2 5

Figure 2: Complications associated with COVID-19 patients with diabetes 17

Figure 3: Myocardial injury in COVID-19 patients with diabetes 18

Figure 4: Cytokine storm in COVID-19 18

Figure 5: Mechanism of action of antidiabetic drugs 28

List of Acronyms

ACE	Angiotensin Converting Enzyme
ARDS	Acute Respiratory Distress Syndrome
ADE	American Diabetes Association
CPRD	Clinical Practice Research Datalink
CGM	Continuous Glucose Monitoring
DKA	Diabetes Keto Acidosis
DI	Diabetes Insipidus
FGM	Flash Glucose Monitoring
GDM	Gastrointestinal Diabetes Mellitus
ICU	Intensive Care Unit
MERS	Middle East Respiratory Syndrome
RAAS	Renin Angiotensin Aldosterone System
SARS	Severe Acute Respiratory Syndrome
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

Chapter 1

Introduction

The biggest crucial story in medical news is COVID-19 since the start of 2019. There is a relatively increasing rate of diabetes-related hospitalization among diabetes patients than the non-diabetics due to COVID-19 infection. Both mortality and morbidity can be relatively high among patients in the hospital compared to those who are not hospitalized after infecting with that disease (Wiersinga et al., 2020). Angiotensin-converting enzyme 2 (ACE2) is the critical receptor for severe acute respiratory syndrome coronavirus (SARS-CoV) and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2. The consequence of the ACE2 receptor is to affect the endocrine part of the pancreas' islet during COVID-19 in patients. When it is about outpatient care, diabetic patients have undergone a dramatic shift in their treatment plan due to the lack of proper clinical management during that global pandemic (Klonoff, 2020). SARS-CoV (2002–2003) and MERS-CoV (2012–2013) were two of the deadliest β– coronaviruses, which caused 10% and 36% of deaths, respectively. Notwithstanding the fact, the majority of human coronavirus infections are fairly benign (Hussain et al., 2020).

There is scientific proof that states about the prevalence of "Coronavirus disease 2019" and all the threats associated with pre-existing chronic health conditions which already have posed a major challenge for both healthcare professionals and patients (Zhou et al., 2020). Type 2 diabetes mellitus affects at least 20% of the 500,000 Belgians, where most of them are over the age of 65 years. It is calculated that more than 3 million people in France are directly affected by type 2 diabetes mellitus (T2DM) and among that 25% of the affected are currently suffering from that fatal infection. According to the International Diabetes Federation (IDF), it is estimated that half of the world's diabetic patients are unaware of their disease and its clinical management during COVID-19 (Guo et al., 2020).

Coronaviruses are single-stranded RNA viruses which belong to the family of Coronaviridae (subfamily Coronavirinae, order Nidovirales). Coronaviruses are divided into four main genera (α, β, γ, & δ) though so many variants of that viruses have already been found (Gao et al., 2021). If the infection is not asymptomatic, coronaviruses only can cause flu-like symptoms in humans, which are self-limiting. Despite the fact, the coronaviruses that cause severe pneumonia necessitate hospitalization, ICU admission, the use of invasive mechanical ventilation that may finally lead to high death rates for diabetic patients. Many COVID-19 infected patients have diabetes as a comorbid condition (Orioli et al., 2020).

World Health Organization (WHO) declared the outbreak of COVID-19 to be a Public Health Emergency of International Concern on the 30th of January in 2020. As a result, countries having fragile healthcare delivery systems should be particularly concerned about that life-threatening infection as it spreads out so quickly (Andersen et al., 2020). If COVID-19 is detected early and is treated appropriately (isolation and treatment approaches), the rapid expansion of that infection can be lessened for diabetic patients. In addition to this, defining the disease severity and the extent of transmission are becoming a critical objective nowadays. Mitigating the economic effect of that deadly virus and countering the globally disseminated erroneous information about that fatal infection is also become crucial parts (Sohrabi et al., 2020).

In many countries of the world, the deadly disease continues to spread out rapidly. Europeans (4,515,514 cases and 222,624 deaths) and Americans (14,117,714 cases and 486,843 deaths) have an increased incidences of COVID-19 compare to the South-East Asia (4,786,594 incidents and 84,541 lives lost), Africa (1,088,093 cases and 23,101 mortalities), or the Western Pacific (4,786,594 cases and 84,541 deaths) (Yan et al., 2020).

1.1 Corona Virus and Its Types

Coronaviruses are enveloped, single-strand RNA viruses with helically symmetric nucleocapsid. They are one of the largest RNA viruses, with an approximate genome size of 26.4 kilobases. The Latin name corona represents the appearance of virions by electron microscope, with vas, tuberculous surface limbs that embody crown-like shape (Wiersinga et al., 2020). Human coronaviruses can lead to a wide range of symptoms, but the intensity of the illness they pose varies greatly. HCoV-OC43, HCoV-HKU1, and HCoV-229E all these known coronaviruses cause minimum symptoms, but SARS and MERS can induce severe, even life-threatening ailments, such as COVID-19 (which is currently being investigated). Infection rates of Human Coronavirus are at their peak usually in spring and winter (Friedman et al., 2018).

1.2 Origin of COVID 19

The first recorded instance of pneumonia was in Wuhan, China in December 2019. After a couple of months, the World Health Organization (WHO) declared this fatal infection as a pandemic (Wiersinga et al., 2020). SARS-CoV-2 also referred to as COVID-19, is the seventh coronavirus to infect people. The virus may use a massive population density as its intermediary host after originating from the reservoir. The target of that virus is to obtain the optimized SARS-CoV-2 RBD (Receptor-binding-domain) region and polybasic cleavage locations to propagate through natural selection. Conversely, as a consequence of zoonotic transmission, the selection procedure could happen in humans continuously (Sohrabi et al., 2020).

On May 10, 2020, 213 countries and regions had received 3,99 million reports of COVID-19 cases, resulting in 2,78,94 deaths (Wiersinga et al., 2020). It started in China and then expanded to the countries like Italy, England, and the United States. Many countries of South Asia and Africa had joined in afterward in the epidemic timeline. Even though the lesser rate of death in Africa can be attributed to that pandemic, but the other leading factors like younger population, favorable climatic factors, other potentially confounding factors and, chronic conditions may have an impact on disease severity over time (Sohrabi et al., 2020). It is terrible that globalization had arrived in SAARC countries (Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka) later compared to Europe and the United States (Sohrabi et al., 2020).

1.3 Pathophysiology of SARS COV-2

Respiratory impairment, the hyperactive inflammatory response is frequent in SARS-CoV-2 disease. In the earlier stage of the disease, the pulmonary and hyper inflammation phases are the notable stages of the SARS-CoV-2 infection. Fever, a persistent cough, and a headache all are common in the early stages of the infection (Lim et al., 2021). Prothrombin, dimeric D-dimer, higher IL-6, lymphopenia, and low LDH are some of the clinical signs and symptoms of the intense infection. The pulmonary phase can be challenging for some patients, with breathing difficulties and unusual chest imaging during that infection (Sohrabi et al., 2020).

Therefore, only a small percentage of the diabetic patients in the more developed, crucial stage of that disease may undergo a "cytokine storm," which can lead to serious complications like acute respiratory distress syndrome (ARDS), shocks, various organ failure, and deaths in the later stages that disease (Gao et al., 2021). Inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin, Troponin, NT—pro-BNP) are elevated during this phase. The degree of illness in patients is influenced by both viral infection and the host's responses to that virus (Erener, 2020).

There are 14 residues in the composition of SARS-CoV-2, which are known to interact with a human angiotensin-converting enzyme (ACE), and 8 of these residues have been conserved in SARS-CoV-2. There are many reports about the one-stranded RNA viruses in humans and other animals, such as chickens, pigs, and other farm animals, as well as dogs and cats. The coronaviruses may be responsible for all serious illnesses (Wiersinga et al., 2020).

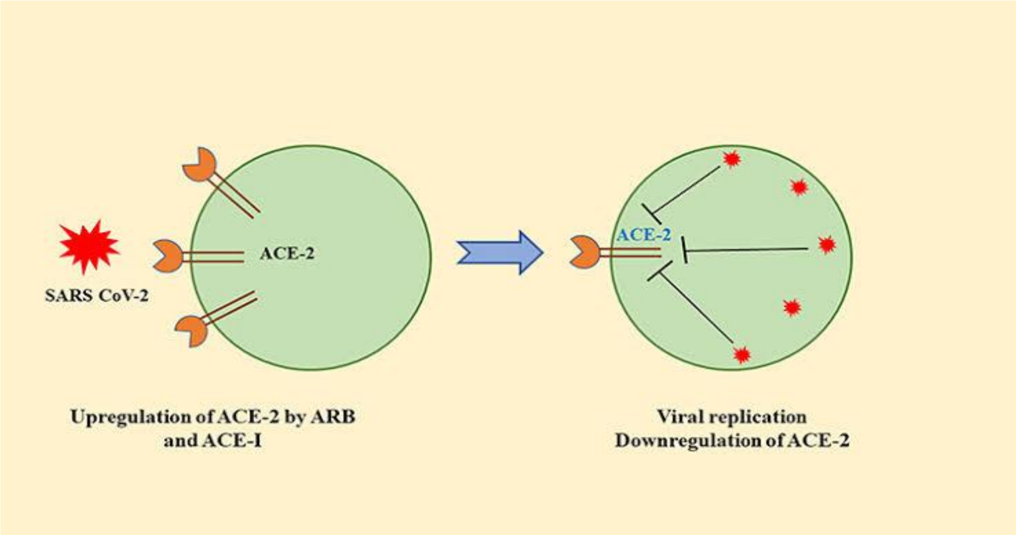

Figure 1: Pathophysiology of SARS CoV-2(Wiersinga et al., 2020).

1.4 Transmission of COVID 19 Worldwide

3.99 million COVID-19 incidents have been documented on May 10, 2020, both in the United States and the United Kingdom (Wiersinga et al., 2020). Following the SAARC countries like Pakistan, India, Bangladesh, Afghanistan, Maldives, Sri Lanka, Nepal, and Bhutan; the greatest number of COVID-19 instances happened in India in 2020. COVID-19 was responsible for the deaths of 2,78,941 people globally, where India had one of the highest death tolls among the SAARC countries (Pakistan, Bangladesh, Afghanistan, Sri Lanka, and the Maldives) (Wiersinga et al., 2020).

Most incidents in SAARC countries may be underestimated owing to the lack of testing equipment and facilities. As per a report, males are more frequent to get infected with COVID-19 in Bangladesh and Nepal which is significantly high than the females, while the opposite is true in Bhutan (44.3% of men, vs. 55.7% of women) (Orioli et al., 2020). While a patient is seriously ill or injured, respiratory viruses are far more contagious than other types of infections during that period. There is evidence that is mounting that human-to-human transmission of COVID-19 can occur during the asymptomatic time of incubation (Zhou et al., 2020). Most of the previous patients having COVID-19 encountered Chinese seafood in Wuhan, China, and wild animal markets referred to as the main origin of that disease. It happened through zoonotic exposure which was an assumption (no proven research document). Bat is not out up for sale in the wild animal market nowadays as it is referred the primary origin of that fatal infection (Zhou et al., 2020). Human-to-human spreading was later discovered in healthcare professionals and others who had no prior contact with that particular infected animal or travels to Wuhan rather than they had contact with the infected hospitalized patients (Andersen et al., 2020).

As per this study, droplets, direct interaction, and aerosols are considered the primary modes of transmission for that virus. Inhaling or ingesting respiratory droplets from an infected individual can spread the disease within even about the distance of 6 feet (Wiersinga et al., 2020). Hand-to-mouth contact with a virus-infected surface or object can also result in a person contracting the disease. The research found that at least 3 hours after inhalation, the virus even can be still spread out through airborne aerosols (Hussain et al., 2020).

1.5 Sign and Symptoms and suspects

Both SARS and MERS-CoV propagate in the lower respiratory tract, leading to pneumonia, intense hypoxic encephalopathy, and respiratory problems, as well as multiple organ failure and shock (in severe cases). Most frequent SARS-CoV-2 adverse effects included dry cough, a runny or itchy nose, and throat, intense form of pneumonia, a high temperature, and respiratory distress (Sohrabi et al., 2020). It is not uncommon for people to die because of developing complications that refer to life-threatening like acute respiratory distress syndrome (ARDS) due to COVID-19 infection. Patients in the stage of critical care are often suffering from diarrhea, dizziness, nausea, malnutrition, shock, etc. (Erener, 2020).

Diabetes, cardiovascular, cerebrovascular, endocrine, and digestive ailments are notable comorbidities among elderly patients who are more prevalent and require intensive care after infecting with the coronavirus. For example, HIV has been characterized by an increased danger of introducing COVID-19 and its clinical manifestations (Sohrabi et al., 2020). Patients over the age of 65 years with diabetes and cardiovascular disease are potentially at high risk for infection. The elderly are more likely to be vulnerable to COVID-19 because of an underlying inflammation state known as inflammatory response, as well as a lack of innate and adaptive immunity, abnormal expression of ACE2, and other COVID-19 pathogenesis-related complications (Marian, 2021).

1.6 Diabetes and Its Types

Diabetes increases the risk of long-term illness and early death. It is reported that one death happens all over the world every 10 seconds. According to the earlier statement, diabetes is a term that is broad which covers a variety abound of medical conditions in which blood sugar levels remain elevated for an extended length of time (Yan et al., 2020). Type 1 Diabetes mellitus (T1DM) is most often seen in children and adolescents (35 years). Inheritance and environmental exposure play a vital role in determining a person's risk of developing diabetes. T2DM refers to a lack of insulin production and release as a result of insulin resistance (Pugliese et al., 2020). Both obese and non-obese people are susceptible to Type 2 diabetes mellitus. Diabetic Gestation Mellitus (GDM) is the onset of diabetes during pregnancy and the remission of the condition happens after the gestation period (Kaul et al., 2012).

Diabetes Insipidus (DI), is the most frequent type of polyuria–polydipsia syndrome, which is characterized by an excess of urination and drinking (more than 3 liters per day). Polyuria after osmotic diuresis disorders (such as uncontrolled diabetes mellitus) can be differentiated between primary and secondary polyuria (which results from primary polydipsia). During pregnancy, gestational DI is the third and rarest form of Diabetes Insipidus that might observe (Crain et al., 2019).

1.7 Prevalence and Severity

Diabetes along with the factors that are risky such as older age, high blood pressure, obesity, smoking, and sedentary lifestyle are associated with the COVID-19 infection. In a global study of 8910 COVID-19 patients, it was found that 14.3% of the patients had diabetes mellitus. COVID-19 non-survivors are notably more prevalent in Asia, Europe, and North America (Bouhanick et al., 2020). Multivariate analysis has found that diabetes is not only associated with inpatient mortality but also outpatient mortality during that pandemic. A severe form of COVID-19 is denoted by the World Health Organization (WHO) as the infected patients having more than or equal 30 per minute of respiratory rate, less than or equal 93 percent saturation of blood oxygen, more than 60 percent lung contribution, as well as having hypoxia, dyspnea within 24 to 48 hours of hospitalization. Diabetic patients who require mechanical ventilation or intensive care unit (ICU) admission indicate great threats or odds ratio of disease severity of COVID-19 infection (Singh & Khunti, 2020).

1.8 Diabetes and COVID 19 Susceptibility

Microorganism-borne diseases have been linked to diabetes because of a dysfunctional immune system response. The number of diabetic patients among the COVID-19 infected patients is quite high all over the world. People with diabetes are slightly more likely to get SARS-CoV-2 as it is considered an immune-suppressed disease (Peric & Stulnig, 2020).

Recent data from patients with COVID-19 demonstrated an independent risk factor for death in SARS and MERS is age. There is a greater prevalence of having diabetes, heart disease, and hypertension in elderly people (Pugliese et al., 2020). This can lead to a decline in the ability of T and B cells to limit viral replication and the prolongation of pro-inflammatory responses, which has detrimental effects on the body's ability to fight infection. When it comes to chronic inflammation, there is a wide range of age-related factors to be considered for that particular virus (Rajpal et al., 2020).

1.9 Rational of The Study

People have died at an unprecedented rate and the economy has been severely disrupted by the virus's global spread from China. Almost two years of paralysis have engulfed the globe. Patients having pre-existing conditions are most prone to suffer from that infection like cardiovascular disease, diabetes, and chronic obstructive pulmonary disease (COPD). Diabetes is a disease that suppresses the immune system's functions. A higher prevalence of getting COVID-19 is shown for people with diabetes than the people of general, but there is evidence that is very inadequate to support this claim. As a result of contracting the virus, a greater risk is tied to diabetes to develop more severe complications. Diabetes, heart disease, and other medical conditions can lead to a serious form of COVID-19. People over the age of 65 are also more likely to suffer complications from the virus. Chances of contracting COVID-19 will be reduced if diabetes is clinically well-managed and treated properly. Therefore, for preventing the dissemination of the virus, diabetic patients must take all necessary precautionary measures and have access to the medical care they need to keep their condition in check and avoid death as well as minimize global loss.

1.10 Aim and Objects of The Study

This study aims to gather elaborate knowledge about the clinical features and other complications that are faced by any diabetic patient during the COVID-19 phase. It will also allow us to manage diabetes and prevent the severity of COVID-19 infection.

The particular objectives of the study are:

- To understand the underlying mechanism of interconnection between COVID-19 infection and diabetes.
- How to lower the risk of illness for COVID-19 patients and reduce the mortality rate.
- How to do clinical management of pathophysiology of diabetic patients infected with COVID-19.
- To create awareness to prevent that fatal disease.

Chapter 2

Methodology

This paper is an overview of the comprehensive look into the association of diabetes with COVID-19. This paper has been constructed based on an outline with relevant research questions per heading. The content for each heading was extracted through a literature search. The information for this review paper was collected from primary sources such as NCBI, Science Direct, Wiley Online Library, Journal of the American Medical Association, etc., and secondary sources such as Pub med, Web MD, Parent Magazine, etc. and tertiary sources like the University of Michigan Health, etc. The plethora of information was then summarized in tabular form to organize the current data available. The mechanisms of action pertaining to the complications and the fatal development were illustrated with appropriate citations of literature. The areas that need further research have been identified and discussed. The use of valid and reliable information with proper in-text citation and bibliography has been meticulously followed using APA reference format.

Chapter 3

Association of Diabetes with COVID 19

According to one of the most significant measures published to date stated that 7.4 percent of COVID-19 patients had diabetes. Moreover, this number was certainly higher among patients with more severe pre-existing illness and those who had undergone the primary outcome and endpoint testing (in an intensive care unit admission, mechanical ventilation's use, or death) due to COVID-19 infection. A total of 8.2% of COVID-19 patients had diabetes as demonstrated by the researchers (Bouhanick et al., 2020). A study found that only 3% of the 1012 patients had diabetes who were not in critical condition during COVID-19. Consequently, 788 COVID-19 patients were divided into two age groups: under 60 and over 60, for determining the disease severity and vulnerability (Huang et al., 2020). The risk of diabetes is unquestionably influenced by COVID-19 patients due to the association of various complications. A study stated that 29.2 percent of the hospitalized diabetic patients already had received insulin therapy, while 37.5% had received oral anti-diabetic therapeutic interventions and then insulin therapy (if it was required) (Guo et al., 2020).

There is a clear indication of poor glycemic control in patients with diabetes while they are in the hospital for having treatment. For example, increased RAAS activity and dysfunction of the sympathetic nervous system all have the potential to contribute to inflammation due to that infection (Rajpal et al., 2020). When SARS-CoV attaches and invades infected cells by using ACE2, Angiotensin II then converts into angiotensin (a synthetic hormone) and that change is responsible for triggering a hyper-inflammatory response in COVID-19 with diabetes. The hyper-inflammatory and hypercoagulable Strom in COVID-19 may be triggered by an excess decline in ACE2 activity, that is already markedly altered in diabetic patients (Tadic et al., 2020). COVID-19 sufferers experience diverse signs and conditions, from minor to severe and even fatal conditions. As an outcome of the COVID-19 pandemic, diabetic healthcare providers suggest the diabetes patients for home quarantine who have mild symptoms. Outpatient diabetes care has been remarkably restructured across the country due to the pandemic (Klonoff, 2020).

Diabetic patients' down-regulated immune responses have a major contribution to worsening aggravation of infection and increasing mortality rate of COVID-19 infected patients. SARS-COV-2 causes pleiotropic alterations in glucose metabolism which in turn complicates the pathophysiology of pre-existing diabetes or direct to new mechanisms of diabetes. Due to the impaired immune response of diabetic patients' higher number of COVID-19 viruses enters into the cell and facilitate severe infection (Tadic et al., 2020). Only one study has examined that acidosis and diabetic ketoacidosis were found in a massive group of COVID-19-confirmed hospitalized patients. It contributes a vital role in the maladaptive immune response to the virus of SARS-COV-2 (Dhatariya et al., 2020). Acidosis and ketoacidosis prevalence in the 658 COVID-19 patients who were hospitalized has been recorded in one research-based study. Diabetic patients are more vulnerable to bacterial infections than non-diabetic patients. It impairs the functions of polymorphonuclear and T lymphocytes as well as the ability of the immune system to fight infection during the COVID-19 period (Gentile et al., 2020).

COVID-19 has been linked to cardiac strain and acute myocardial injury for diabetic patients. It has been observed that COVID-19 patients with diabetes boost the risk of the severe progression of infection ranging from a minor symptom to the life-threatening one (Selvin & Juraschek, 2020). Cardiac disease was found in 8 percent of COVID-19 patients, which was linked with a growing incidence of death (Singh & Khunti, 2020). An increase in insulin-related biomarkers, such as IL-6 and D-dimer has been observed in diabetic patients, which is stating the development of chronic inflammatory response that ultimately results in the degradation of COVID-19. High glucose level activates pro-inflammatory cytokines and adhesion molecules that promote tissue inflammation, which is resulting in an increased level of oxidative stress and tissue damage. Sepsis, pneumococcal pneumonia, SARS, MERS, and H1N1 flu all have been linked to diabetes and hyperglycemia (Rajpal et al., 2020). SARS-CoV-2 infection exacerbates preexisting chronic inflammation by increasing the viral load in many cells throughout the body. Cytokine storm occurs when elevated levels of interleukin-6 (IL)-6 in the bloodstream are noticed during SARS-CoV-2 infection in diabetic patients (Peric & Stulnig, 2020).

According to a recent New York City on the COVID-19 incident series, there were 5,700 patients where diabetic patients are more likely than the non-diabetics to require invasive ventilation support in the intensive care unit (ICU) (Miles et al., 2020). Diabetic patients have significantly thicker alveolar epithelium and capillary basal lamina than non-diabetic patients. Consequently, during the period of COVID-19, the pulmonary complications could be exacerbated by an infection due to COVID-19 which may decrease respiratory function (Erener, 2020).

SARS-CoV-2 can trigger a "cytokine storm," which can result in serious illness. A "cytokine storm" is an indication while the immune system is overreacting. Previous SARS and MERS coronavirus had revealed the presence of pro-inflammatory cytokines and chemokines such as IFN-, IL-1B, IL-6, and IL-12 in higher levels. COVID-19 patients' high death rate may be due to the "cytokine storm" and delayed inflammatory response which is caused by SARS-CoV-2 infection (Pugliese et al., 2020). Underactive defense system in diabetics is noted with infrequent cytokine responses and exaggerated numbers of immune cells. Additionally, it is feasible that high blood glucose levels are interfering with viral replication. Severe disease advancement in COVID-19 is characterized by interferon-gamma latency, delayed hyperinflammatory state, and decreased CD4+ and CD8+ cell numbers. Diabetic patients are unable to detect and eliminate pathogens due to the lack of chemotaxis and phagocytosis (Erener, 2020).

Diabetes has been linked to the deterioration in the condition of health during COVID-19. The immune and inflammatory responses are impacted by hyperglycemia and an imbalance in these responses has resulted in severe COVID-19 patients. Endothelial dysfunction occurs when endothelial cells are unable to function effectively (Liu et al., 2020). Endothelial inflammation, which is driven by diabetes, is associated with greater cytokine storms and respiratory abnormalities. Infection of endothelial cells can be accomplished by SARS-CoV-2 easily through the ACE2 receptor (Pugliese et al., 2020).

Patients with diabetes who contract COVID-19 infection are more vulnerable to organ ischemia, tissue necrosis, and increased pro coagulation due to a shift in vascular tone toward vasoconstriction. Upregulation of hypercoagulation and fibrinolysis markers, as well as elevated platelet activities and rigidity to the endothelial wall, can lead to hyperinflammatory conditions like SARS-CoV-2 infection in diabetic patients. As an outcome, blood clots can form in a variety of places in the body during the infection period (Erener, 2020).

Table 1: Complications Associated to COVID-19 patients with diabetes.

Name of complications	**Consequences due to the pathogenesis**	**References**
Diabetic ketoacidosis	Hypokalemia, pulmonary edema, respiratory distress, maladaptive immune response, multiple organ damage, which all lead to the increased rate of mortality	(Gentile et al., 2020)
Diabetes and Infection Risk	Peripheral nerve damage, respiratory distress, urinary tract infection, soft-tissue infection, lowered blood flow, impaired immune system, all of that are responsible for a higher mortality rate	(Peric & Stulnig, 2020), (Erener, 2020)

Cardiac dysfunction	Damaged blood vessels, acute myocardial injury, damaged lung tissues, chronic inflammatory response, hyper-inflammatory, and hyper-coagulable storm, cardiac biomarkers above the 99% upper reference limit are closely aligned to death rates	(Tadic et al., 2020), (Peric & Stulnig, 2020)
Hyperglycemia	Increased viral replication in pulmonary epithelial cells, tissue inflammation, increased oxidative stress, tissue damage, prolonged cytokine response, sepsis, pneumococcal pneumonia all leads to higher mortality	(Hussain et al., 2020), (Orioli et al., 2020)
Chronic Inflammation	Increased cytokine storm, dysfunctions of the innate immune system, insulin resistance, decreased cell activity, increased viral load, increased oxidative stress, which all cause a great number of deaths	(Rajpal et al., 2020) , (Peric & Stulnig, 2020)
Hypertension	Insulin resistance, acute respiratory distress syndrome, respiratory failure, intense infections that all may result in a higher number of deaths	(Rajpal et al., 2020)
Alveolar Dysfunction	Reduced respiratory functions (alveolar membrane permeability, total pulmonary volume, compelled vital capacity, lowered compelled pulse rate), increased vascular permeability, collapsed alveolar epithelium, thicker alveolar epithelium, and capillary basal lamina are closely aligned to breathing difficulties that lead to greater death rates	(Erener, 2020)
Dysregulated Immune Response	Delayed hyperinflammatory state, reduced innate and adaptive immune responses, elevated levels of IL-6, ferritin, ESR, CRP, chronic inflammation, lowered	(Pugliese et al., 2020)

	IFN-1, which may facilitate more viral replication and lead to death	
Cytokine Storm	Overactivation of the innate immune system, hyper-inflammatory response, delayed inflammatory response are the causes of the highest death rates	(Pugliese et al., 2020) (Erener, 2020)

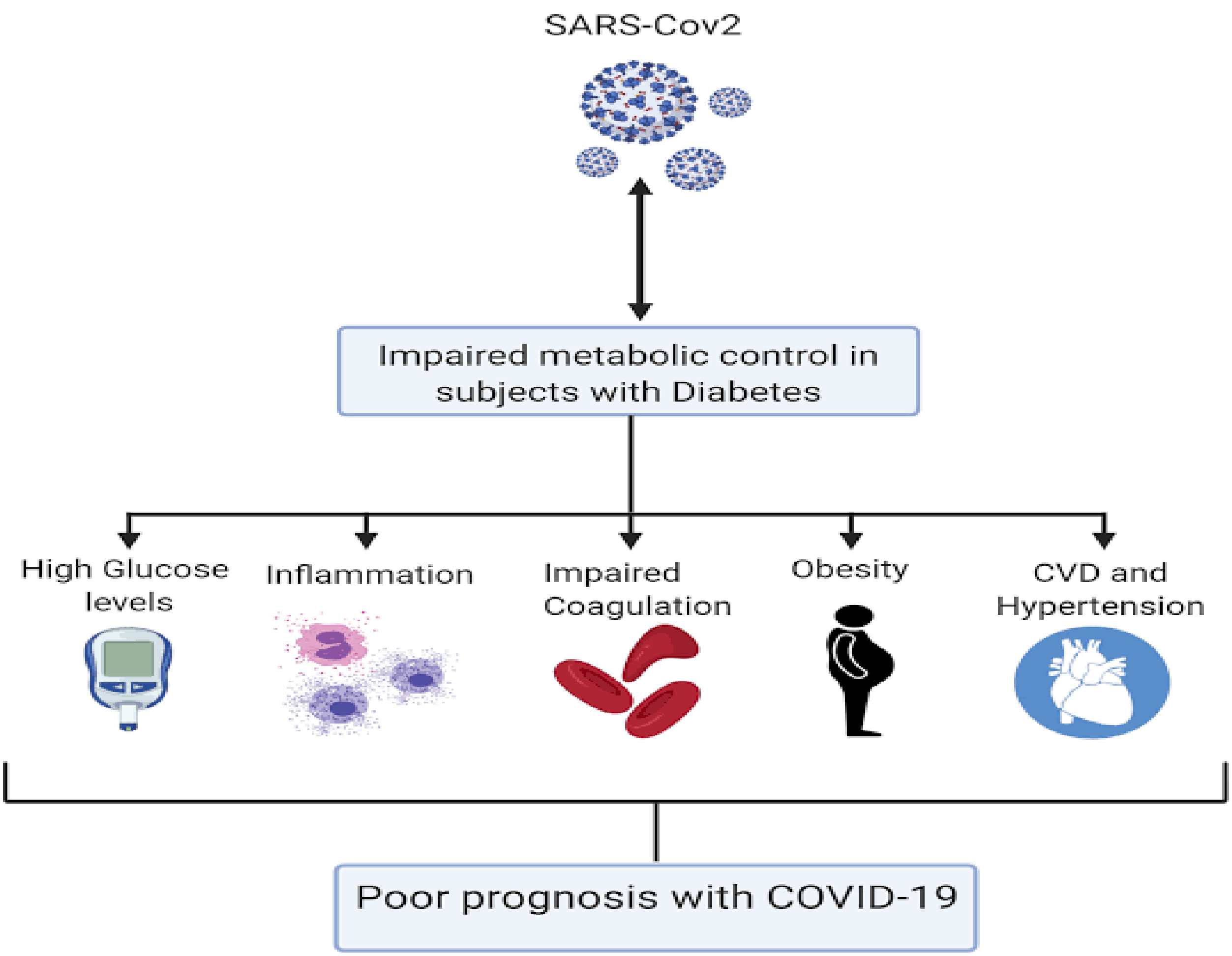

Figure 2: Complications associated with COVID-19 patients with diabetes(Guo et al., 2020)

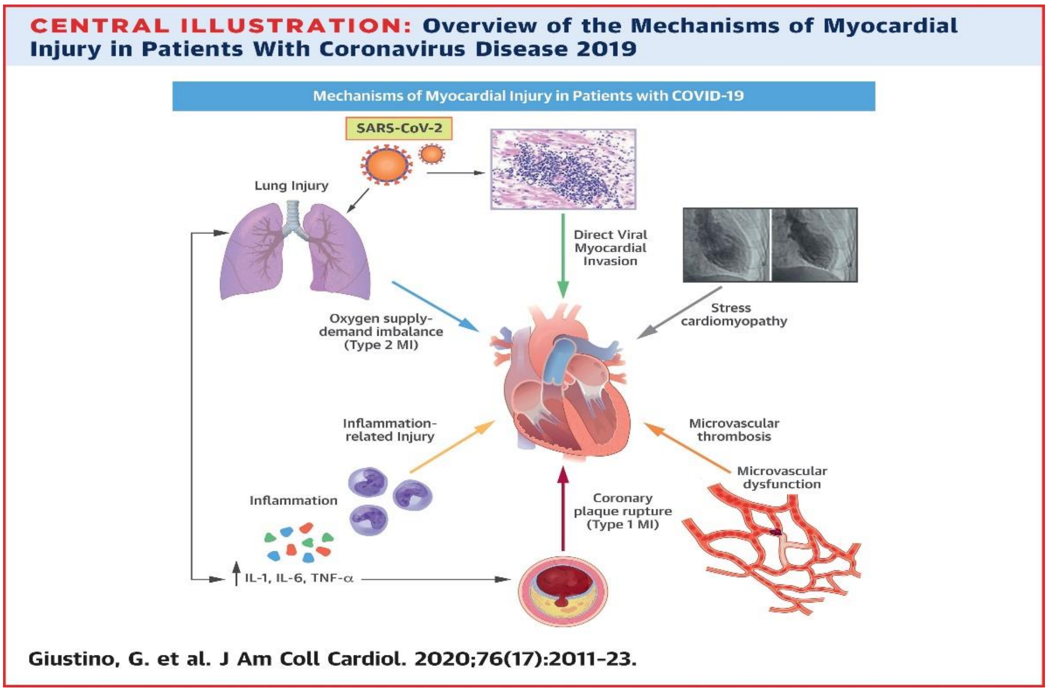

Figure 3: Myocardial injury in COVID-19 patients with diabetes (Erener, 2020)

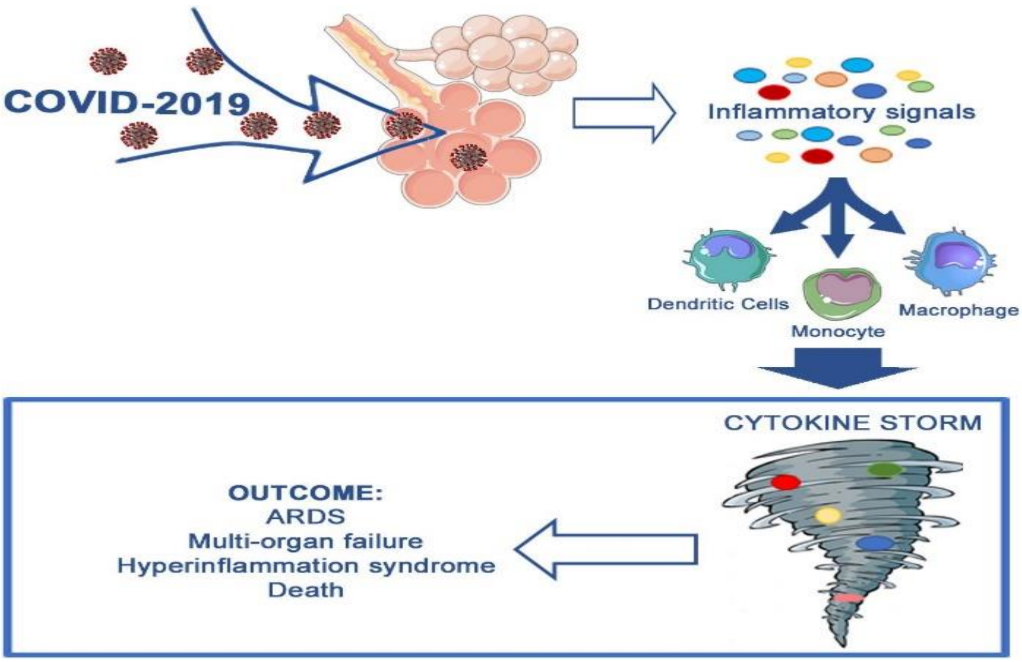

Figure 4: Cytokine storm in COVID-19(Pugliese et al., 2020)

imbalances in these processes. (Pugliese et al., 2020) Endothelial dysfunction occurs when endothelial cells are unable to function effectively. Endothelial inflammation, which is driven by diabetes, is associated with greater cytokine storms and respiratory abnormalities. Infection of endothelial cells by SARS-CoV2 can be accomplished through the ACE2 receptor. Patients with diabetes who contract COVID-19 infection are more vulnerable to organ ischemia, tissue necrosis, and increased procoagulation due to a shift in vascular tone toward vasoconstriction. Diabetic upregulation of hypercoagulation and fibrinolysis markers, as well as elevated platelet activities and rigidity to the endothelial wall can lead to thrombotic events under hyperinflammatory conditions like SARS-CoV-2 infection. As an outcome, blood clots can form in a variety of places in body (Erener, 2020).

Chapter 4

Diabetes-Related Comorbidities

The severity of COVID-19 in patients with diabetes may occur due to pre-existing comorbid conditions as well as hyperglycemia. Kidney disease, obesity, and high blood pressure are all comorbidities of metabolic syndrome, which is caused by chronic hyperglycemia. As per the study, SARS-CoV2 patients were also found to have chronic kidney disease (CKD) and cardiovascular disease (CVD), including coronary heart disease (CHD), heart failure (HF), and cerebrovascular disease (CVR) as pre-existing diseases (Singh & Khunti, 2020). According to a report by the China Center for Disease Control, 12.8 percent and 4.2 percent of COVID-19 incidents were found to have high blood pressure and cardiovascular disease respectively. Two national surveys on COVID-19 hospitalized Chinese patients found the prevalence rates of hypertension of 15.0% and 16.9%, CHD/CVD of 2.5% and 3.7%, cerebrovascular disease of 0.4% and 1.9%, and chronic kidney disease (CKD) of 0.7% and 1.3% (Mirani et al., 2020). As a result, patients with more severe conditions and those who accomplished a composite outcome are more likely to have hypertension, heart disease, cerebrovascular disease, and chronic kidney disease. According to several meta-analyses, the prevalence of diabetes, cardiovascular, cerebrovascular, and chronic kidney diseases (CKD) was significantly higher to increase the intensity of infection in patients with COVID-19 (Pugliese et al., 2020).

4.1 Mortality

China's 44,672 infected patients died at a rate of 2.3 percent, while the mortality rate for diabetics and hypertensives was 7.7 percent and 6 percent, respectively. Diabetic patients were found in 35 percent of the corona virus-infected people (Singh & Khunti, 2020). Diabetes was thus overrepresented among 70 percent of people where men with an average age of 80 years were observed mostly. Research shows that diabetes is linked to an increased mortality rate due to the COVID-19 infection (Bouhanick et al., 2020). For both hospitalized and non-hospitalized diabetic patients in Belgium, COVID-19 has been linked to a higher mortality rate. 15 percent of diagnosed Belgians had died, among that 45 percent of those deaths occurred in hospitals and the rest of the deaths occurred at-home care services (Bouhanick et al., 2020).

It was found that the total mortality rate of COVID-19 in China was 2.3%, while the mortality rate of diabetic patients was greatly noticeable. Research conducted in China and Italy found that COVID-19 patients who were critically ill or died had chronic illnesses along with diabetes at their core. In a study, patients with various comorbidities were found to have a growing risk of ICU admission, Intermittent mandatory ventilation use, and/or death (Orioli et al., 2020).

According to an observational study, patients with diabetes and/or uncontrolled hyperglycemia (defined as blood glucose values >180 mg/dL within any 24 hours) were significantly more likely to die (28.8%), while those patients without diabetes were less likely to die (6.2%) due to that fatal infection (Banerjee et al., 2020). Between February 1, 2020, and April 25, 2020, the NHS England's COVID-19 Patient Notification System (CPNS) continued study on 17,425,445 adults and recorded 5683 COVID-19 deaths (Singh & Khunti, 2020).

Chapter 5

Diagnosis of COVID-19

Health services for the COVID-19 are available in SAARC countries for diagnosis of that virus. According to WHO, only India is missing from the list of countries in the SAARC region that have tested for SARS-CoV-2 by their followed recommendations. Real-time reverse transcriptase PCR (RT-PCR) is used to detect the presence of COVID-19. Screening for SARS-CoV-2 in upper and lower respiratory samples is done by using SARS-specific primers and probes (Hussain et al., 2020).

Moreover, due to a lack of resources and facilities, most SAARC countries then had collected samples from patients suspected of being COVID-19 positive based on empirical diagnosis, travel history in the affected states, or from those who have had close contact with the infected person (Singh & Khunti, 2020). Many false COVID-19 results were noted due to the proper diagnosis procedure. To detect COVID-19, maximum countries use RT-PCR and rapid tests which are based on antibodies. Following table details the testing procedure, testing facilities of a few countries. India had conducted 1,610,788 tests on 10th May 2020; while the Maldives had the highest test capacity (1659,446 as of May 10th,2020 (Wiersinga et al., 2020).

Table 2 : COVID-19 tests and testing facilities in SAARC countries as of May 10, 2020

Name of country	**Test Name**	**Collected samples**	**Reference**
India	RT-PCR, Antibody-based Test, True Nat Test, CBNAAT Test.	Swab, sputum, nasopharyngeal swab, bronchoalveolar lavage (BAL) or endotracheal aspirate for RT-PCR; Blood/serum/plasma, nasal/throat	(Wiersinga et al., 2020)
Pakistan	RT-PCR Test	Nasopharyngeal or oropharyngeal swab	(Wiersinga et al., 2020)

Maldives	RT-PCR Test	Lower respiratory specimens (sputum, endotracheal aspirate, BAL fluids) and URT samples (nasopharyngeal aspirate or combined oropharyngeal swabs)	(Hussain et al., 2020)

Chapter 6

Treatment Options for COVID 19 Patient with Diabetes

It is not transparent whether diabetes-specific initiatives like intravenous insulin, glucose monitoring, or specific pharmacotherapies can affect the progression of disease severity in diabetic individuals and COVID-19 or not. Treatments available for adults with type 2 diabetes include both ACE inhibitors and angiotensin II receptor blockers (ARBs) during COVID-19 infection (Peric & Stulnig, 2020).

Anti-inflammatory drugs, such as ACE2 inhibitors, increase the virus' ability to attach and infect cells because it has an abundance of ACE2 receptors at its disposal. As a result, the risk of COVID-19 infection may be reduced by using anti-viral drugs, insulin regimens, effective anti-diabetic drugs during the period of intensive care. Vaccination is playing a vital role to mitigate the rate of getting infection and death (Hussain et al., 2020). Angiotensin-converting enzyme-2 (ACE2) has been linked to anti-diabetic medications, which has prompted some of the questions linking COVID-19 and ACE2. Both diabetic and COVID-19 users have no reason to believe that their medications are harmful (Selvin & Juraschek, 2020).

Counseling with diabetologists, nutritionists, and infection managers online may play a vital role to manage COVID-19 clinically. Self-isolation, proper maintenance of hygiene, avoiding crowded places, monitoring of blood glucose levels might be more effective during COVID-19 (Lim et al., 2021).

Table 3: Treatment options for COVID-19 patients with diabetes.

Treatment options	**Treatment**	**References**
Antiviral drugs	Lopinavir, Ritonavir, and Oselectamivir, as well as quinolone prophylaxis, were prescribed specially for treating that COVID-19 infection in the hospital	(Hussain et al., 2020)
Insulin	Insulin is the first choice in the event of an emergency and can be suggested to use for hospitalized diabetic patients with an oral intake that poor or respiratory support might need IV insulin infusion with required time monitoring and control in all of the COVID-19's stages	(Singh & Khunti, 2020)
Vaccine	mRNA and vaccines based on DNA technologies are used such as Moderna, mRNA-1273, Pfizer/BioNTech, Covishield (Oxford/AstraZeneca formulation) all are the vaccine that is being administered nowadays	(Lazarus et al., 2021)
ICU	ICU is required for the high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation when the condition of the patient worsens due to that COVID-19 infection	(Miles et al., 2020)

Table 4: Choosing Anti-Diabetic Drugs During COVID-19

Drugs names	**Mechanism of action**	**Effects**	**Reference**
Metformin	Decreased hepatic glucose production, lowered glucose absorption in the intestine, and elevated uptake of peripheral glucose, as a result, enhanced sensitivity of insulin, that all actions are done by Metformin	Lowered active tuberculosis, glucose-lowering efficacy, lowered risk of hypoglycemia as well as lowered risk of death are observed	(Katsiki & Ferrannini, 2020), (Mirabelli et al., 2020)
Pioglitazone	Selectively stimulated peroxisome proliferator-activated receptor gamma (PPAR-$_{\gamma}$) as well as (PPAR-α) to a lesser extent and genes involved in the control of glucose and lipid metabolism are transcript by the modulation of this drug	Reduced steatohepatitis and production of proinflammatory cytokines, increased expression of ACE2 in hepatic tissue are obtained	(Singh & Khunti, 2020)
DPP-4 inhibitors	Blocked action of DPP-4 enzyme that helps to destroy incretin hormone and the production and reduction of insulin all are done by incretin whenever it is required	Lessened respiratory tract infection, increased insulin secretion, decreased gastric emptying, all of these effects might receive	(Mirabelli et al., 2020)

SGLT-2 inhibitors	The kidney is helped to prevent the glucose reabsorption back into the blood, decrease the glucose level in the blood, and excrete excess glucose through urine which all are done by that drug	Lowered blood glucose levels, improved insulin sensitivity is obtained	(Mirabelli et al., 2020), (Katsiki & Ferrannini, 2020)
GLP-1 receptor agonists	Reduced body weight, enhanced glycemic parameters, increased release of insulin, and lowered release of glucagon in the pancreas all is done by activating the GLP-1 receptors	Elevated heart and lung ACE2 readings, anti-inflammatory, improved blood glucose control all are therapeutic effects of that drugs	(Singh & Khunti, 2020), (Katsiki & Ferrannini, 2020)

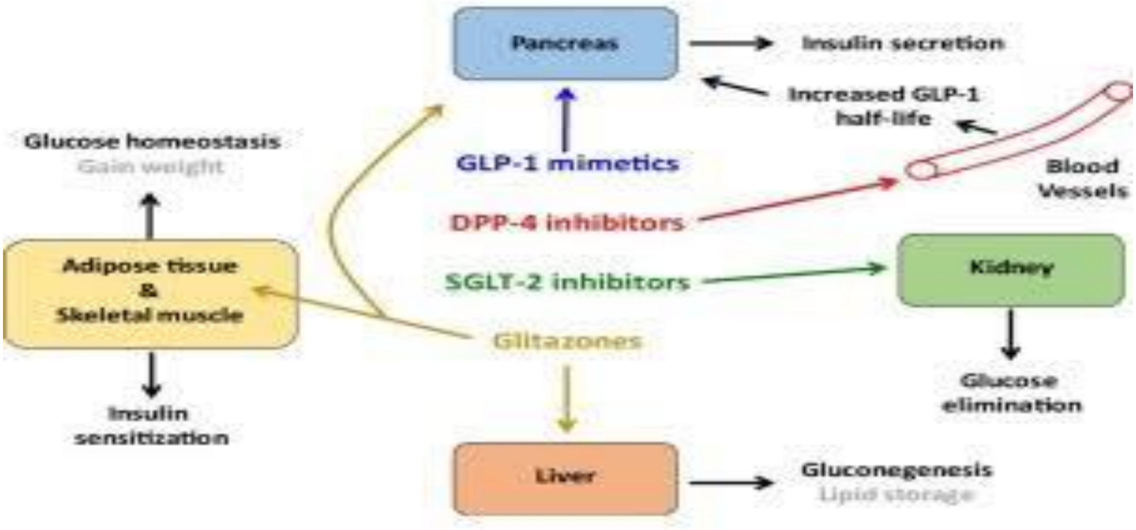

Figure 5: Mechanism of action of antidiabetic drugs (Mirabelli et al., 2020)

6.1 Care for COVID 19 Patients Who Has Diabetes

Diabetic patients who are treated outside of a hospital setting need to have social isolation and quarantine in consideration. The inability to get a routine check of the level of blood glucose has become noticeable due to the reduced outpatients' clinic capacity. Requiring someone to stay at home certainly might result in getting less exercise than they would usually get regularly. As a result, it is reasonable to assume that calorie balance would improve in a portion of subjects during that time (Peric & Stulnig, 2020). Glycemic control may suffer as a result of more calorie intake and less physical activity. Increasing the frequency of blood glucose measurements has become critical for patients with type 1 diabetes during isolation due to pandemics. Many diabetes treatment facilities have also been affected by the COVID-19. For preventing the disease from spreading, many hospitals have reduced the capacity of their outpatient care, doctors' chamber visits, and improved medical care (Hussain et al., 2020).

Insufficient glucose control during the COVID-19 pandemic has left the healthcare systems to be vulnerable to both acute and long-term health issues for diabetic patients. Alternatively, telemedicine with upgraded devices can be used as a supplement to diabetes management. However, insulin, oral diabetes medications, and glucose management therapies are still readily available in the SARS-CoV-2 pandemic (Peric & Stulnig, 2020). Physicians monitor the normal range of blood glucose levels of diabetic patients by using flash glucose monitoring (FGM) and continuous glucose monitoring (CGM) during COVID-19 with a little time requirement. Insulin therapy is commonly used in hospitals to treat both diabetics and critically ill patients. Insulin is the first choice in intensive care units because other glucose-lowering medications should be discontinued then (Wiersinga et al., 2020). Extra caution is required to avoid hyperglycemia. Glycemic control may be exacerbated by both the lockdown's effect on lifestyle choices and the COVID-19 infection. A regular schedule of doctor visits and blood glucose monitoring is recommended for all diabetic patients (Bouhanick et al., 2020).

6.2 Self-management

An ongoing method of developing the knowledge, expertise, and capacity are needed to effectively manage diabetes is referred to as diabetes self-management education (DSE). It has been shown to enhance the good care quality for diabetic patients which is an important part of self-care (Peric & Stulnig, 2020). The American Diabetes Educators (AADE) has identified seven self-care patient behavioral patterns (eating of healthy food, intake of medicine, physical activities, critical thinking, risks reduction, proper monitoring, healthy coping) as the valid result measures for self-management education for diabetes (Banerjee et al., 2020). National Task Force of Diabetes Self-Management Education and Support has established the national standards for diabetes self-care (Hussain et al., 2020).

6.3 Diet

India's diet is already rich in carbohydrates, and they're also cheap. Carbohydrates are accounted for 64.1 percent of the total calories that are usually consumed by 796 people who have type 2 diabetes mellitus (T2DM), which is quite higher than the permissible level in India. Lockdown-related food shortages are assumed to lead to an increase in carbohydrate consumption. Indians have a particular fondness for sugar-sweetened beverages and foods. To help diabetic patients to keep their health in check, here are a few tips below: (Banerjee et al., 2020).

- Starting any diet program requires figuring out how many calories need to consume each day. There should be a caloric intake of 20-kilo calories per kilogram for obese patients and 22 to 25-kilo calories per kilogram for those who are not overweight but are physically inactive. Indian dietary guidelines recommend dividing the total daily caloric intake into three meals and an evening snack.
- At least 50-60 percent of total calorie intake should come from carbohydrates; for example, 225-270 grams of carbohydrates should be consumed daily by an average Indian person who is sedentary.
- Any type of cereal grain can be eaten. 25-40 grams of dietary fiber per day is an ideal amount to consume. Fresh fruits and vegetables are rich sources of dietary fiber because they contain a high amount of water.
- Foods that are high in sugar, such as juice of different fruits, alcoholic beverages, and sugar syrups, must be avoided. Animal fats should be limited to not more than 30 percent of total calories consumed each day and should be consumed in minimum amount.
- Choosing low-fat milk would be best (Banerjee et al., 2020).

- Meal preparation should use not more than three teaspoons of oil per day. Cooking oil made from a mixture of two or more vegetable oils would be ideal.
- An Indian vegetarian's recommended daily protein intake is 1 g/kg in a day. A reduced intake of red meat is needed (Banerjee et al., 2020).
- Sodium chloride intake should be limited to not more than 5 grams in a day, and the traditional practice of Indians of sprinkling additional raw salt on food should be abandoned.
- The insatiable thirst for sugary tea (especially at home) needs to be curtailed. Tea should be consumed often without sugar.
- Dietitians will also be able to keep in touch with patients via web counseling. Clinical trials have shown that telemedicine-delivered dietary interventions can improve dietary quality, the number of fruits and vegetables consumed, and sodium intake.
- Betel chomping, excessive tea and coffee consumption, and smoking are dangerous habits that should be avoided at all costs (Banerjee et al., 2020).

6.4 Physical activity

Individuals with diabetes would be severely restricted in their ability to participate in outdoor fitness activities if a lockdown or even a complete shutdown were imposed. Consequently, they should be made aware of other forms of physical activity they can engage in without having to leave the comfort of their residence during that pandemic (M. Banerjee et al., 2020).

- It is recommended that adults engage in 60 minutes of physical activity each day, which is divided into aerobic training, work activities, and muscular activity.

- The goal is to get moderate-intensity aerobic activity at least for half an hour each day. Taking a walk on the roof of a building or in the grass at a pace that makes talking difficult but not impossible.
- A treadmill could be used if it is available. In addition to stationary jogging, stationary biking, and growing vegetables, flowers, aerobic activities such as these could also be implemented.
- If aerobic exercise is done twice or three times a day, it needs to break into 15-minute increments.
- Stair climbing and domestic chores, which require 15 to 20 minutes of daily exercise, are examples of work-related activities.
- Muscular exercises, such as push-ups, sit-ups, crunches, and forward flexion exercises (such as light weightlifting), should be done for at least 15 minutes every day.
- Yoga and other exercises for increasing flexibility and mobility of the joints are also part of the curriculum. If the exercise is too strenuous or physically taxing, then it should be modified (Banerjee et al., 2020).

Chapter 7

Conclusion & Future Recommendation

Diabetes is associated with an increased risk of intense COVID-19 infection as the coronavirus leads to pleiotropic alterations in glucose metabolism which direct to the development of complications due to new mechanisms of diabetes than the preexisting one. Diabetes suppresses the functions of our immune systems; the virus easily can propagate and facilitate severe infections. Anti-infective measures remain the most effective way to prevent that infection including medications that lower the sugar levels in the blood, vaccine administration that reduces the chance of getting that fatal infection. Hospital care should be more improved, and healthcare professionals must especially focus on the monitoring of blood glucose levels, insulin regimen, and the upgraded effective treatment strategies to lower the complications associated with COVID-19 patients with diabetes as well as the death rate.

COVID-19 continues to receive a great deal of research and clinical attention because now it is common in the whole world and because its negative effects on diabetic patients are so well documented. Although there have been advances in research and clinical care on many fronts, the pathophysiology of different variants of that fatal virus still needs further research to acknowledge. Mechanism of actions of that pathogenesis which are related to the rise of various complications in diabetic patients needs to be documented. The efficiency and risk factors of the COVID-19 vaccine that are administered to diabetic patients are needed to be studied further. There are still questions to be answered about the efficacy of antidiabetic drugs, during the period of COVID-19. Early screening, insulin regimen, monitoring of blood glucose, effective anti-diabetic drugs, and proper ventilation need to be focused on to decrease the severity of the COVID-19 patients with diabetes.

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