A Review on Association Between Respiratory Infections and Diabetes

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Declaration

It is hereby declared that,

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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.

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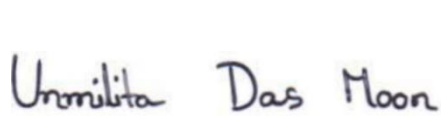

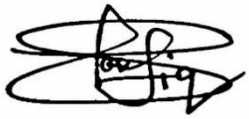

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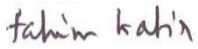

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Abstract

Respiratory disease is a major cause of elevated morbidity and mortality worldwide. Between 1990 and 2017, the mortality rate from chronic respiratory diseases increased by 18%, from 3.32 million to 3.91 million. Several studies have reported that people with diabetes have a significant rate of respiratory infection. This review evaluated the association between diabetes and multiple respiratory diseases such as Tuberculosis, Influenza, and Covid-19. Diabetes patients are often immunocompromised. Their health deteriorates further as they are exposed to respiratory infections, which result in serious health problems such as coronary complications, hyperglycemia, pulmonary vascular abnormality, renal impairment, pancreatitis, endothelial dysfunction, and inflammatory infiltration. In the case of tuberculosis, diabetes patients experience more disease complications than non-diabetics. Tuberculosis can result in infection-related hypoglycemia and hyperglycemia in diabetic patients, altering the immune response to tuberculosis, which causes further hypoglycemia and hyperglycemia-related complications. Moreover, diabetes patients show a less positive response to tuberculosis therapy. Due to influenza, diabetes patients become more vulnerable to a lung infection that might cause damage to myocardial tissues, ultimately resulting in cardiovascular complexity. So far, the evidence does not support that the SARS-CoV-2 infection rate is higher in diabetic patients. However, increased severity of SARS-CoV-2 infection is observed in diabetic patients. Increased viral entry, higher inflammation levels, and reduced T cell function have also been reported in SARS-CoV-2 infected diabetic patients.

Key Words: TB, Influenza, SARS-CoV-2, Diabetic, Hyperglycemia, Pancreatitis, Hypoglycemia, Immunocompromised, Endothelial Dysfunction, Inflammatory Infiltration, Cardiovascular Complexity, Myocardial Tissues, T Cell.

Dedication

To Our Family

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List of Acronyms

TB- Tuberculosis

DM- Diabetes mellitus

CD4- Cluster of Differentiation 4

Th1- T Helper Cell Type 1

Th17- T Helper Cell Type 17

WBC- White Blood Cell

AMI- Acute Myocardial infarction

HBA1C -Hemoglobin A1C

SARS-CoV-2 -Severe Acute Respiratory Syndrome Coronavirus 2

ACE2- Angiotensin Converting Enzyme 2

HIV- Human Immunodeficiency Virus

CRP- C Reactive Protein

T2DM- Type 2 Diabetes Mellitus

ICU- Intensive Care Unit

T Cell- Thymus Cell Lymphocytes

DKA- Diabetic Ketoacidosis

IL-6- Interleukin-6

PAI-1- Plasminogen Activator Inhibitor-1

A Review on Association Between Respiratory Infections and Diabetes

Chapter: 1

Introduction:

Respiratory diseases have been one of the significant causes of mortality and morbidity worldwide. The mortality rate from chronic respiratory disorders accelerated by 18% between 1990 and 2017, increasing from 3.32 million to 3.91 million.[1] Respiratory disease is a condition of the respiratory process that affects the structural elements and organs involved in breathing by causing diseases and disorders of the air passages and lungs, which negatively impact human respiration and eventually lead to complexities in breathing due to the sudden decrease of oxygen levels in the blood. [2, 3] This type of infection can be classified as Upper Respiratory tract Infections and Lower Respiratory Tract Infections. Respiratory disorders were reported in 26 %, 21 %, and 13 % of people with type 1 diabetes, type 2 diabetes, and no diabetes, respectively. [4] Diabetes has been found as significant comorbidity that increases the risk of morbidity and mortality associated with different respiratory disorders. The lung is a target organ that is affected by the complications of type 1 and type 2 diabetes. [5] Moreover, Diabetes is currently a critical public health concern that is constantly expanding in an epidemic proportion worldwide. [6] It is a chronic metabolic disorder that develops once the pancreas is no longer capable of producing insulin or once the body cannot form an effective use of the insulin it contains. The failure to generate or use insulin with efficiency leads to higher blood glucose levels outlined as hyperglycemia. [7] In 2019, a WHO report stated that almost 463 million individuals worldwide have Diabetes, and 1.6 million deaths are directly correlated with Diabetes every year. Both the number of cases and the prevalence of Diabetes are rapidly increasing over the past few decades. [8] Diabetes can be classified into two types that are: Type 1 diabetes and Type 2 diabetes, along with another type which is Gestational Diabetes that occurs only during pregnancy. There is an inherited form of Diabetes known as monogenic Diabetes as well as cystic fibrosis-related Diabetes, which are less common. [9, 10] Diabetes can significantly elevate the threats of heart attacks and strokes in adults two- to three-fold and decreased blood flow alongside neuropathy in the feet, which increases the possibility of foot ulcers, sepsis, and consequent limb amputation. [11, 12] Even the lung functions get impacted by

Diabetes, such as the individuals who have type II diabetes their lower lung volumes get decreased about 3% to 10%. [13] A further concern is systemic inflammation which is a severe condition with Diabetes that is associated with endothelial dysfunction, can lead to obstruction of airflow. [14] Also, the epigenetic regulation of Diabetes has been associated with oxidative stress, non-enzymatic protein glycation, and the polyol pathway, which might cause lung injury. [15] Besides, Diabetes is associated with reduced pulmonary elasticity and carbon monoxide transport capability. From other research, it has been found that approximately 10% of all disability-adjusted life is because of respiratory disease. [16] In this review, we assessed different respiratory diseases like Tuberculosis, Influenza, Covid-19 effect on Diabetes. We have analyzed if this respiratory disorder increases morbidity and mortality in diabetics patients. We also have assessed the mechanisms of these effects.

Chapter: 2

Tuberculosis and Diabetes:

Tuberculosis is a severe contagious infection caused by bacteria known as *Mycobacterium tuberculosis*, which provokes damage to the lungs and other areas of the body, such as the brain, spine, etc. Developing TB is higher in patients with diabetes than non-diabetics as diabetic patients have a weak immune system. [17]

In 2019, almost 10 million people were diagnosed with TB, and 1.4 million individuals died. Moreover, approximately 465000 were newly diagnosed with drug-resistant TB. [18] People with inadequate immune systems, particularly those with rheumatoid arthritis, HIV infection, diabetes mellitus, severe renal infection, cancer, stomach ulcers, and those who have had a gastrectomy, are at a much higher risk of contracting TB disease than people with standard immune systems. [19, 20] *M. Tuberculosis* infection can manipulate the human microbiome, which has a strong association with immune stability and health. [21] TB is an airborne disease transmitted from person to person through the air, and physical contact does not transfer the bacteria until it is breathing in. [22, 23] This causative agent usually resides inside the host lung and prolificate; later, using the blood, it spread into the different parts of body like the brain, spine, and kidney.[24]

A report of 2019 has presented that overall diabetic patients are 20.7% more prone to have TB than regular patients. Another study showed that TB infects 7.7% of type 2 diabetic patients out of 0.8 million reported cases in 2016. [21, 25] Clinical research has demonstrated that patients with DM have three times more risk of active TB than non-DM cases and can experience morbidity. [26, 27] In **Table 1**, we summarized the prevalence of the patients with Diabetes mellitus (DM) infected by TB from several studies based on different countries. From **Table 1** comparison can be done between the status of TB patients with Diabetic and non-diabetic patients. Studies have proven that active TB patients with DM have increased CD4+, Th1, and Th17 responses but reduced natural regulatory of Treg cells or T cells frequencies relative to patients without DM. [28] Whereas DM patients with latent TB have inversely decreased Th1 and Th17 responses compared to patients without DM. [29] Diabetic patients have a compromised immune system which makes DM a more significant risk factor for TB. [30] From a meta-analysis, it is found that diabetes has a relative risk of 3.11 of contracting TB. [31] Patients with concomitant TB and DM may have a higher rate of fever and Hemoptysis. [32] Hemoptysis is a severe health condition that can be life-threatening as it causes damage to airways by rupturing and resulting in bleeding with cough.[33] From this information, we can relate to those diabetic patients as they have a higher chance of having TB, resulting in life-threatening conditions. It is found in research that diabetes induces pulmonary vascular abnormalities such as endothelial dysfunction, inflammatory infiltration, and pulmonary vascular remodeling.[34] Moreover, DM and TB have a bi-directional relation as TB can cause new diabetes cases by impaired glucose tolerance in TB-infected patients. [35, 36, 37] In **Figure-1**, we can see that TB causes hypoglycemia due to a drop in glucose level. Hypoglycemia can lead to patients losing consciousness, seizures, and worst-case scenario result in death. Impaired glucose resistance is characterized as two-hour glucose levels 7.8 to 11.0 mmol on the 75-g oral glucose resilience test. The hindered fasting glucose is characterized as glucose levels 5.6 to 6.9 mmol per litter in fasting patients.[38] These glucose levels are better than average yet beneath the level that is indicative for diabetes. Furthermore, TB is a known cause of Pancreatitis, as active tuberculosis should be a differential diagnosis in patients with enlarged pancreas and Pancreatitis that might reveal itself only after the development of diabetes. [39, 40] Pancreatitis is inflammation in the pancreas, which causes dysfunction of the pancreas as the pancreas produces proteins that help in absorption and chemicals control the way body measures sugar. [41] Having much sugar in the blood for significant periods can cause

genuine medical issues if it is not treated. [42] On the other hand, Hyperglycemia alludes to significant degrees of sugar, or glucose, in the blood. When the body does not deliver or utilize sufficient insulin, a chemical that ingests glucose into cells for use as energy, Hyperglycemia happens. [43] Hyperglycemia can hamper the vessels that supply blood to vital organs, expanding the danger of coronary illness and stroke, kidney failure, vision issues, and nerve issues [42]. TB can lead to infection-related Hyperglycemia, which may mimic DM and the Hyperglycemia associated with TB, often by aggravating the glycemic control of diabetics. [39] **Figure 2** described that Tb patients who have diabetics could be infected by Pancreatitis. This will be the outcome of dysfunction of the pancreas resulting in Hyperglycemia. This Hyperglycemia causes coronary illness, strokes, kidney failure, vision issues, never issue. From this evidence, we can understand that Tuberculosis (TB) is a genuine health threat, particularly for individuals living with diabetes.

Country	TB Patients	Age Range (years)	TB Patients With Diabetes	TB Patients Without Diabetes	Effects of TB on Diabetic Patients	Reference
America	44	40–58	22	22	DM is associated with an alteration in the immune response to tuberculosis.	[28]
America	90	28–65	60 (DM and Pre-DM)	30	DM or pre-DM, is characterized by diminished production of cytokines	[29]
Indonesia	737	39-52	94	540	DM is associated with a less favorable response to TB treatment.	[31]
Serbia	889	20-88	88	801	The number of individuals with DM can easily get infected by TB	[44]
Nigeria	4000	12–85	480	3520	Patients with DM and TB comorbidity had higher WBC	[45]
Southern Mexico	1262	15<	374	888	Frequency and progression health risks of diabetes mellitus patients	[46]

Table 1: Prevalence of Diabetic patients infected by TB.

TB Impaired Glucose Resistance

↓

Drop glucose Level

↓

Hypoglycemia

↓

Loss of consciousness, seizures, or death.

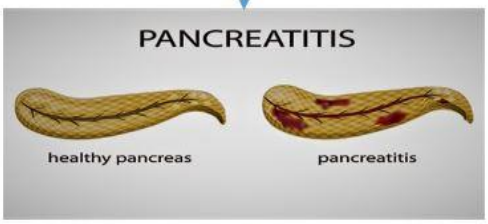
Figure 1: TB causing hypoglycemia in diabetic patients (30, 34 and 35)

TB Cause Pancreatitis

↓

Activated Pancreatitis
In Present of Diabetic patience

↓



[79]

↓

Dysfunction of Pancreas

↓

Hyperglycemia

↓

Coronary illness, Stroke,
Kidney sickness, vision issues,
Nerve issue

Figure 2: TB causing hyperglycemia in diabetic patients (34, 35, 36, 37, 39, 40, and 42)

Chapter: 3

Influenza and Diabetes:

Influenza is one type of enveloped virus that belongs to the family Orthomyxoviridae and has RNA segments containing negative-sense and single-strand. Moreover, Influenzas are four types: A, B, C, and D; however, only genera A and B are clinically relevant for humans.[47]

A CDC report stated that the United States estimated 60.8 million cases related to the (H1N1) pdm09 virus. Among them, there were 274,304 cases of hospitalizations and 12,469 cases of deaths.[48] Influenza infections are spread mainly through airborne contamination and usually droplets like 5 μm which can be produced while talking, sneezing, or sniffling; thus, small distances of contact is used to enter the mucosae. [49] Influenza A infections are found in numerous various creatures, including ducks, chickens, pigs, whales, ponies, seals, and cats, but Influenza B infections flow broadly just among people. [48, 50]

Generally, influenza infection is self-restricting contamination; however, in people who have a previous persistent disease, such as diabetes mellitus, severe influenza can develop.[51] In **Figure 3a** and **3b**, we present the comparison between influenza patients with diabetes and without diabetes. It is stated in **3a** that patients without diabetics do not have myocardial tissue death, wherein **Figure 3b** in a diabetic patient, influenza infects the lungs and destroys the myocardial tissue, and causes cardiovascular sickness, resulting in death. Some influenza prescriptions contain non-steroidal mitigating drugs, for example, ibuprofen, which is not typically suggested for individuals with diabetes since they may marginally build the danger of heart issues and stroke. [52] It is discovered that people who has diabetes are three times more likely to have respiratory disease given as a cause of death than non-diabetics. As influenza is a regular flu, it is the most common respiratory disease known. [53] Glucose levels can affect the seriousness of an Influenza infection disease such as hyperglycemia which is identified with the most noticeably awful result in bacterial and viral diseases. [54] An investigation showed a nonlinear relationship between glucose guidelines and HBA1C flu (influenza) mortality. [55] Another factor is cardiovascular sickness, causing an expanded occurrence of intense myocardial dead tissue (AMI) after respiratory contamination, especially in the flu season. [56] Due to all these risk factors of the

Influenza virus and the chances of diabetes to have an influenza infection, it is high in probability for that particular purpose influenza, and diabetes combine can be very dangerous.

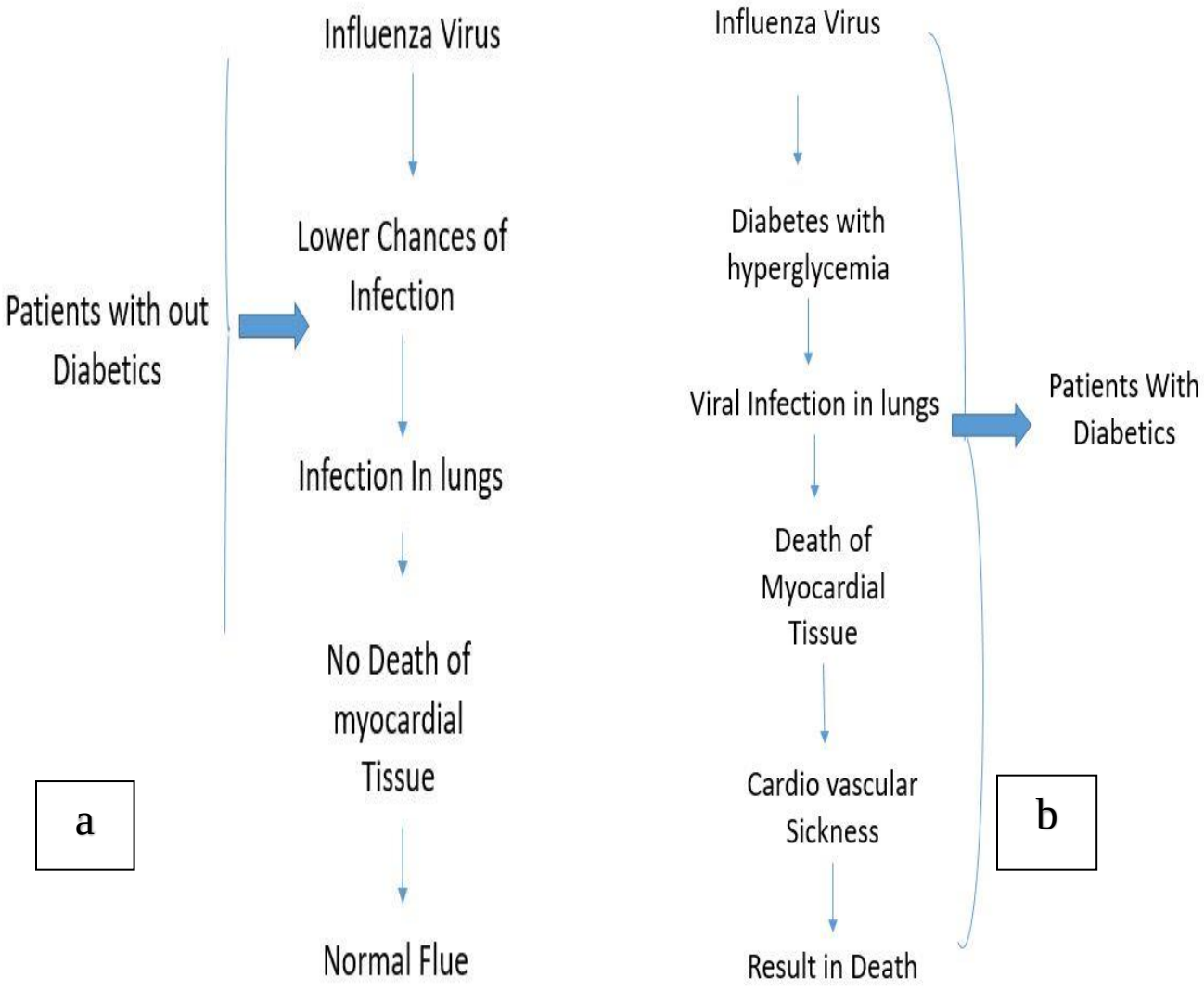


Figure 3: Influenza virus combining with diabetics causing myocardial tissue death. 3a: Influenza Virus in non-Diabetic patients (49, 51). 3b: Influenza Virus in Diabetic patients (51, 52 53, 54, 55 and 56)

Chapter: 4

Covid-19 and Diabetes:

A coronavirus is a form of the widespread virus in the nose, sinuses, or upper throat that causes an infection. In early 2020, it emerged after an outbreak in China in December 2019, and gradually it spread throughout the world. In this Covid-19 disease by SARS-CoV-2 severe respiratory tract infection is occurring. [57] An infected person transmits the virus through droplets or saliva by coughing or sneezing, and its incubation period is within 14 days of exposure to the virus. [58] Numerous SARS-CoV-2 infected people would develop mild to moderate respiratory disease and recover without any special care. However, severe respiratory morbidity and mortality among older people can be caused by SARS-CoV-2, as well as the individuals who are suffering from different types of medical conditions such as cardiovascular disease, Diabetes, chronic respiratory disease, and cancer. [59, 60] Till February 2021 approximately 113,991,689 cases of infection and 2,529,421 case of death due to SARS-CoV-2 has been reported. [61] It has been found in research that comparing individuals without diagnosed Diabetes, the death ratios of people with type I Diabetes were 3·51, and the death ratios of people with type II diabetes were 2·03. [62]

Diabetes is considered a chronic metabolic disorder, and because of it, excessive blood sugar fluctuation is being believed as a risk issue for SARS-CoV-2 virus disease.[63] In **Table 2**, we summarized the research based on the different countries that revealed the prevalence of the SARS-CoV-2 virus among the patients with Diabetes. As coronavirus (SARS-CoV-2) can infect with an extreme acute respiratory syndrome, the virus proteins bind to receptors called angiotensin-converting enzyme 2 (ACE2) that usually helps in regulating blood pressure which is seen in major metabolic organs and tissues such as adipose tissue, kidneys, pancreatic beta cells, small intestines as well as glucose metabolism-related pleiotropic alterations which are considered as the pathophysiology of preexisting Diabetes that SARS-CoV-2 causes.[64] According to research, significant coagulation formation with severe SARS-CoV-2 sepsis is usually correlated, including an inflammatory response to cytokine production stimulated by viral invasion. [65] The attribution of inflammatory markers such as adiponectin, C-reactive proteins, IL-6, leptin, *PAI-1*, and tumor necrosis factor α is used to determine the role of inflammation in Diabetes. [66]

Diabetes rendered SARS-CoV-2 sufferers quite vulnerable to an inflammatory storm, ultimately resulting in significant deterioration of SARS-CoV-2 patients. They had higher CRP levels, neutrophils, and procalcitonin but decreased lymphocyte rates compared to non-diabetic patients. [67] Moreover, counter-regulatory hormonal responses, the impairment of β-cell function with the inflammatory cytokine storm, acute metabolic deterioration, hyperglycemia, increased cellular binding affinity, and efficient viral entry, decreased viral clearance, reduced T-cell function by combining with Diabetes can worsen SARS-CoV-2 outcomes. [68, 69] As diabetic patients have compromised immune system for combating against the virus because of reduced insulin output and as Diabetes keeps the body in a low-level state of inflammation by decreasing blood flow which caused difficulties for transporting nutrients to protect against infections and prevent the healing process. [70] In **Figure 5**, the diabetic patients going through high-level inflammation. This causes the white blood cell to decrease, causing metabolic disorder. In the end, it is clearly stated that hypoglycemia cellular binding affinity increases. The infection rate increases because of viral entry and reduction of T cell function. Moreover, obesity is closely linked with Diabetes which is associated with a chronic low-level state of inflammation exacerbated by SARS-COV-2 and enhances the prognosis of diabetic patients suffering due to SARS-CoV-2. [71] Another concern for SARS-CoV-2 infected patients is a significant reduction in insulin affected by diabetic ketoacidosis or DKA that restrains cells from using glucose for energy and burning fat or even producing ketones in the blood, which can be lethal.[72] Diabetes increases the probability of SARS-CoV-2 fatalities and occurrence. With this information combined, we can conclude that SARS-CoV-2 can be highly lethal and deadly for diabetic patients.

Country	Covid-19 Patients	Median Age	Diabetes	Effects of SARS-CoV-2 on Diabetic Patients	Reference
Saudi Arabia	439	55 years	68.3%	DM patients have a significantly higher death rate and lower survival time	[73]
America	5700	63 years	33.8%	Patients with diabetes were more likely to have obtained intensive ventilation or ICU treatment than people without diabetes.	[74]
China	193	64 years	24.9%	Compared with survivors with diabetes, non-survivors had longer diabetes duration	[75]
Italy	355	79.5 years (mean age)	35.5%	The presence of these comorbidities like diabetes might have increased the risk of mortality independent of SARS-CoV-2 infection	[76]
China	339	69 years	16.0%	The incidence of comorbidities was relatively higher in the elderly SARS-CoV-2 patients compared with the whole population	[77]
Saudi Arabia	300	50 years	47.4 %	The prevalence of T2DM is very high and is the most common comorbidity among hospitalized SARS-CoV-2 patients	[78]

Table 2: Prevalence of Diabetic patients infected by SARS-CoV-2.

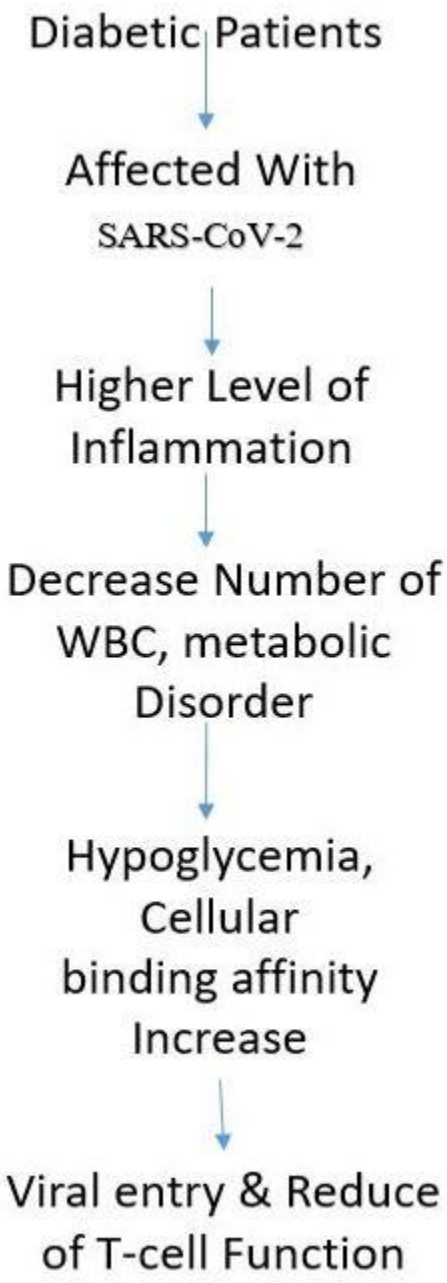


Figure 4: Effect of SARS-CoV-2 in diabetes. In diabetic patients, SARS-CoV-2 enters and causes reduction of T cell (63, 64, 65, 66, and 67)

Chapter: 5

Conclusion and Perspectives:

There are several impressive proofs that diabetes is a danger factor and an alarming condition deteriorated by Tuberculosis, influenza, and covid-19 disease. Though debilitated invulnerability close by impeded kidney, Pancreatitis, hypoglycemia, lipotropic etc. – highlights the severity of diabetes. All these respiratory diseases for people with diabetes is resulting in high mortality and morbidity.

In our perspective, as there are 463 million people who have diabetics, all of them must be vaccinated before they can get any of this respiratory disease. There are few arguments that if their weak immune system will cope with the vaccine, it is necessary for our perspectives. The respiratory disease mainly spread or transmitted through infected persons droplets and saliva, so it is safe for people to wear mask always. It is highly recommended that people with diabetes check or monitors their heart rate, oxygen level and glucose level because these are vital media to indicate if they have an infection or not, also; if they are infected, they should be highly monitored by doctors and take prescribed medications as it has been seen diabetes are not allowed or have the same type of medicine as usual patience because of their health conditions. By follow up additional research and studies, it can assume that there is still a wide gap between what we know and what we practice preventing all the complication regarding debates. However, it is possible to lower the chances of getting diabetes by maintaining a proper healthy lifestyle. Overall, efforts are needed to diagnose, treat, and prevent diabetes from living a health sound life.

Chapter: 6

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