New positive β strand RNA virus is causes of diabetes and other disorders.

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Abstract:
The COVID-19 epidemic is currently one of the biggest issues facing our planet. Some people with recently discovered diabetes have been demonstrated in studies to fall between 2 and 3 waves. When COVID-19 reaches pancreatic cells and binds with ACE-2 inhibitors on the inside of the membrane, it destroys it and prevents the β-cell from secreting insulin. COVID-19 promotes cytokines pro-inflammation, which fuels the growth of diabetes. According to the recommendations, biomarkers aid in the early detection of diabetes and COVID-19 patients as well as the selection of appropriate therapies. Results displayed Diabetes, immunological dysfunction, and organ loss were all induced by COVID-19. Patients with COVID-19 were able to identify certain outdated medications because there was no specific medication or vaccination for COVID-19 at the time, therefore older treatments were used on COVID-19 patients.

Key words: T1D (type 1 diabetes), T2D (type 2 diabetes), corona virus (COVID-19) (SARS-COV-2), biomarkers, immune derangement, oxidative stress, endothelial dysfunction, neurological outcomes, eyes diseases, renal diseases, drug therpy.

1. Introduction:

The first COVID-19 cases were discovered in the Chinese city of Wuhan. People were initially labeled as pneumonia patients, but after causative studies revealed a new RNA beta virus, it was renamed accurate respiratory syndrome coronavirus-2 (SARS COV-2)[1, 2]. The World Health Organization (WHO) published the data in July 2021 for cases 1,84,324,026 and 3,922,680 deaths, with cases 535,836,950 and 6,314,972 continuing in 2022 [3]. COVID-19 is an RNA virus structure with a size of about 30Kb that can be transmitted. It can be seen through a virus electron microscope.

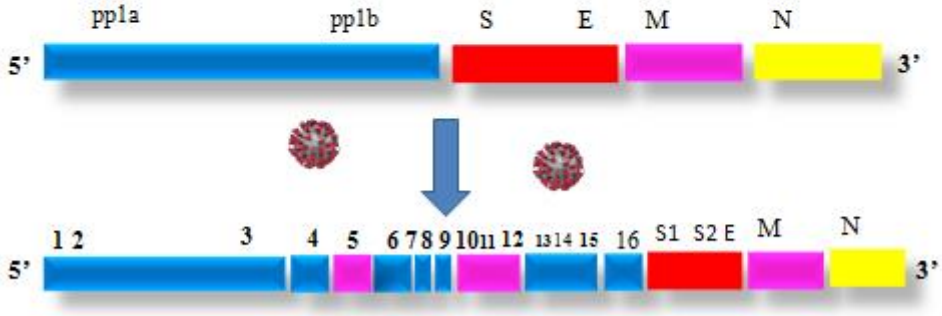

FIG 1 is genetic studies: in this figure SARS-COV-2 infection.

According to recent studies, COVID-19 is a nonstructural protein,(fig 1) the polyprotein PPla and PPlab end code study by ORFs-1a and 1b at 5'-end in two or third the total genome side and end code 3' is distinct six protein 21 to29Kb. There are ORF7b is a presumed apoptotic factor, ORF6 is a presumed IFN-1 antagonist, ORF7a is a presumed leukocyte modulator ORF7b and ORF8 is a presumed 62 immune modulator, and ORF10 is known to function including four structure protein glycoprotein (S), envelop protein (E), membrane glycoprotein (M), and nucleoprotein (N) [4]. Each protein serves a specific purpose: N protein binds to the RNA genome to form the nucleocapsid; S protein is a homotrimer with two subunits (S1 and S2) that are required for binding to host cell receptors; and E protein interacts with M to form the viral envelope, whereas M protein is important in CoV assembly and viral envelope shape regulation. These proteins possess significant antigenic epitopes and are responsible for host cell adhesion and subsequent disease [3, 4**]**.

Numerous genes, including MTNR1B, LC30A8, THA ADA, TCF7L2, KCNQ1, CAMK1D, CDKAL1, IGF2BP2, HNF18, and CENTD2, have been linked to decreased β-cell function, whereas PPARG, FTO, and LLF14 have been linked to increased insulin sensitivity. When increased fasting glucose results in impaired insulin sensitivity, which raises the risk of developing diabetes, and HOMA-B and HOMA-IR.

COVID-19 is a member of the corona virus family. COVID-19, unlike other corona viruses, causes infection in humans. Corona that causes humans is a 229E, NL63, OC43, and HKU10 [5]. Recently, studies have shown that SARS-COV-2 binds to ACE-2 on the cell's outer membrane and damages it, then enter the pancreatic cell, damaging the β-cell and decreasing insulin secretion, resulting in diabetes, including type 1 and type 2 diabetes. SARS-COV-2 infects pancreatic cells, causing pro-inflammatory cytokines that cause diabetes.

T1D, an autoimmune disease caused by a shortage of insulin, destroys pancreatic cells [6]. Numerous studies have revealed that enteroviruses, Coxsackie B, Coxsackie A, Echo, CMV, rotaviruses, and retroviruses are also implicated with type 1 diabetes [7-9]. However, current research has discovered that COVID-19 is a single-strand RNA that enters the body and attaches to ACE-1 membranes in several types of cells, causing type 1 diabetes (DKA). According to research, newly diagnosed DKA after COVID-19. According to certain statistics, DKA was a substantial risk factor for children under the age of five who have been admitted to the hospital. Barron et al [10]and Holman et al[9] compared risk T1D and T2D during COVID-19 infection addressing risk factor glycemic control. Their study's outcome is Patients with type 2 diabetes Mellitus (T2DM), obesity, hypertension, cardiovascular disease, and other non-transmissible illnesses have a higher risk of severe COVID-19 and mortality [11,12]. Furthermore, HbA1c and fasting plasma glucose (FPG) levels are independent predictors of COVID-19 mortality and severity [13, 14]. Similarly, mechanistic studies have revealed that MERS-COVID-19 (Middle East respiratory syndrome-related corona virus) infection is linked to chronic hyperglycemia, immunological dysregulation, and sensitivity to severe lung sickness [15].

COVID-19-associated diabetic patient biomarkers are useful for acute treatment. According to the guidelines fasting plasma glucose or plasma glucose or HbA1, CRP [16], IL-6 [17,18], PCT [19], LDH [20, 21], AST–ALT [22], coagulation marker D-dimer [23], NT-proBNP [24] and Troponin T [22] Measurement for COVID-19 and diabetic patients [25].

Several investigations have demonstrated that COVID-19 is linked to diabetes in the long term, producing chronic illness or hypoxia and, as a result, immunological deregulation, chronic inflammation, and chronic endothelial dysfunction [26].

One of the most difficult issues for clinicians is managing COVID-19 patients. At the current time, several diabetic medicines and therapies, such as metformin, sulfonylureas, DDP-4, GLP-1, and insulin treatment, are used to control the health of diabetes patients. According to the statistics, this drug and therapy resulted in a positive outcome for COVID-19-linked diabetic patients [27,28].

2. Material and method:

A lot of publications on COVID-19 and diabetes are accessible on Google Scholar. I analyzed up to 100 research and review papers and presented the findings. This review explains how COVID-19 causes illnesses and how to utilize biomarkers to identify effective therapy.

3. Epidemiology and history:

3.1 diabetes history

According to research, a physician in Egypt and Hesy-Rd described frequent urination as a sign of an unknown illness that also caused emaciation around 1552 BC. The first time, this urine draws diabetic ant species. This test is called a "WATER TESTER," and people with this kind of sickness have sweet urine. The word "MELLITUS" is Latin for "Honey with Diabetes." Scientists developed a chemical test for diabetes in the 1800s to look for sugar in the urine. Scientists have recommended diet and exercise to relieve excessive urine throughout the 1700 and 1800 century [29].

3.2. Genomics of type 2 diabetes:

T2D is our pancreas doesn’t produce too much insulin or resist insulin. The long-term effects of T2D lead to chronic illness because of blood-stream sugar circulation. Diabetes, renal disease, and immunological and brain system disorders are all brought on by high blood sugar levels. Increased thirst, frequent urination, increased appetite, weight loss, weariness, recurrent infections, and discolored skin are some of the symptoms of T2D.

Type 2 diabetes itself is thought to be a polygenic disorder that develops due to the complexity between multiple genes and environmental factors. T2D is mainly two genes CAPN10 is cystine end codes protease is part of the calpain family. Its first risk factor of T2D and second is TCF7L2 is a strong linkage single was mapped to chromosomes [30].

When indices of β-cell function (HOMA-B) and insulin sensitivity (HOMA-IR) derived from paired fasting glucose and insulin measures try and identify the function most affected by various T2D risk genes, it was found that risk alleles at ten loci there are MTNR1B, SLC30A8, THAAD, TCF7L2, KCNQI, CAMK1D, etc. shown in this all type reduced β-cell and PPARG, FTO AND KLF14 were reduced insulin sensitivity. The study of heritable variations in gene function that take place without a change in the nucleotide sequence is known as epigenetics. The cell employs the processes of DNA methylation, histone acetylation, and non-coding RNAs to regulate gene expression in response to environmental stimuli. These mechanisms can last a lifetime, be passed down through two to three generations, and aid in the emergence of chronic disease [31].

Recently studies have shown that around 462 million, or 6.28% of the population, are estimated to have type 2 diabetes today. According to current research, 70% of patients do not have a familial link to type 2 diabetes, and 40% of a person's family is at risk. Pregnancy and intrauterine are the two causes of this kind of patient diabetes [32, 33].

3.3. Genomics of type 1 diabetes:

According to the database 8.4 million and about 95% of people get affected by the diabetes type-1. Of which 1.5 million (18%) people are younger than 20 years, 5.4 million about 64% of people are 20-59 years get affected by type 1 diabetes [34, 35].

T1DGC studies by international research on diabetes type 1. According to that research, genetic resources are responsible for T1D [1]. T1D is an autoimmune disease that leads to the destruction of insulin-producing β-cell. T1D is lifelong insulin replacement therapy, and without insulin lead development o T1D and diabetes ketoacidosis (DKA) [36].

T1D is mainly in three stages. The first stage is non-symptomatic in this stage normal fasting of glucose and normal glucose tolerance and the presence of greater than two antibodies. The second stage is diagnostic criteria including the presence of greater or equal 2 pancreatic antibodies. This stage is also known as dysglycemia impaired fasting of glucose (glucose range between 100 to 125 mg/dl) or impaired glucose tolerance (2PG of 140 to 199 mg/dl) or hemoglobin A1C between 5.7% to 6.4%. The last stage, often known as hyperglycemia, is characterized by clinical signs and the presence of two or more antibodies.

Most studies' outcomes are genetic disposition multiple genes are responsible for causing type 1 diabetes, especially DRB103-DQB10201 and DRB10401-DQB10302H and other antibodies such as Islet cell cytoplasmic antibodies (ICA), Antibodies to insulin (IAA), Glutamic acid decarboxylase (GAD-65), IA-2 (insulinoma-associated protein 2) and protein tyrosine phosphate antibodies and zinc transporter is the causing T1D.

Some causes are developing T1D without any family history [37-39]. This type of diabetes is caused in children born time mothers with COXSACKIEVIRUS and ENTEROVIRUS develop during pregnancy, and other environmental factors and dietary factors such as cow milk protein and low moderate risk HLA-DR.

4. Newly diagnosed type 1 diabetes after COVID-19.

Recent investigations have shown that SARS-COV-2 patients have been diagnosed with diabetes despite having no prior history of the condition [40]. β-cell loss and subsequent insulin insufficiency are symptoms of type 1 diabetes, an autoimmune illness. Food poison or viral infection is examples of environmental causes that might result in it. The SARS-COV-2 positive sense single-stranded RNA virus causes type 1 diabetes. SARS-COV-2 enters the body through many organs and affixes to ACE-2 (fig 2). Hemoglobin A1c (Hb1Ac) raises the risk of diabetic ketoacidosis (DKA) or type 1 diabetes when it binds to numerous organ cells in the body when a virus enters the body and damages those cells, as well as psychiatric disorders, stress, a poor socioeconomic situation, and an elevated level of glyco hemoglobin. Increased CD-8+ cell activation and the development of autoimmune bodies against insulin, glutamic acid decarboxylase, tyrosine phosphatase, and islet cells are two effects of SARS-COV-2 [41]. Develops T1D as a result of autoimmune depletion.

COVID-19 includes excessive circulating levels of pro-inflammation like IL-1, IL-6, IL-7, IL-8, IL-17, IFN-8, TNF-8, CXCL-10, and MCP-1 monocytes chemo attractant protein-1 (MCP-1) and causes acute respiratory distress syndrome (ARDS) [4,43]. The presence of IL-IB promotes the inflammatory response [44]. T1D patients believe that oxidative stress causes an increase in the creation of ROS and that AGEs cause the establishment of the NF-KB pathway [45] and that ROS is superoxide (O2), hydrogen peroxide (H2O2), hydroxyl radical (OH-), and oxygen (1/2 O2). This is all a byproduct of mitochondria, and it has a significant negative impact on T1D. Hussain et al. [46] showed substantial hypersecretion of IL-1α and TNF-α from PBMCs both in 29 T1DM children and their healthy first-degree relatives.

More importantly, in a case-control study from the EURODIAB Prospective Complications Study of 543 individuals with T1DM, plasma levels of CRP, IL-6, TNF-α, VCAM, and E-selectin were significantly higher in patients with macrovascular complications compared to those without [47], suggesting the role of chronic inflammation in the pathogenesis of diabetic micro- and macrovascular complications, which, in turn, have been considered the major risk factor of adverse COVID-19 outcomes.

5. Newly diagnosed type 2 diabetes after COVID-19.

Type 2 diabetes is previously covered in section 2.2. 1. The second form of diabetes is typically induced by severe illnesses such as influenza and pneumonia [48, 49]. However COVID-19 2 OR 3 waves in 2020 to 2021major complication of type 2 diabetes. Hyperglycemia (T2D) has been linked to MERS-COV-2 and SARS-COV-2. SARS-COV-2 enters the body using the same processes. (fig 2)Patients first raise their blood glucose levels, which causes oxidative stress and inflammation. Second, SARS-COV-2 binds to ACE-2 and destroys the tissue, and third, hyperglycemia impairs lymphocyte proliferation. SARS-COV-2 increased stress and glucose levels in individuals via glucocorticoid and catecholamine production.

When SARS-COV-2 attaches to the membrane's outer side, it damages the membrane. After entering the cell, it damages plasma and urine cells. Recent research has revealed some people with newly discovered diabetes following SARS-COV-2 infection. This sort of patient's RAS plays a crucial role in maintaining fluid balance, electrolyte homeostasis, blood pressure management, and vascular function. Then, activation of the ACE-ANG-II/AT1R axis caused vasoconstriction, hypertrophy, fibrosis, and proliferation. The RAS and ACE-2/Angiotensin-(1-7)/MAS AXIS are thrown off balance when SARS-COV-2 binds to ACE-2, which is found in many cell membranes and causes a variety of organ damage. The identical procedure on pancreatic cells and the main effects of insulin. SARS-COV-2 infections may also enhance metalloprotease-17 and disinterring (ADAM-17). Which include insulin resistance and inflammation caused by the production of different cytokines that promote inflammation (TNF- and IL-6). This entire set of factors harms beta cells and results in insulin deficiency (fig) [50-55].

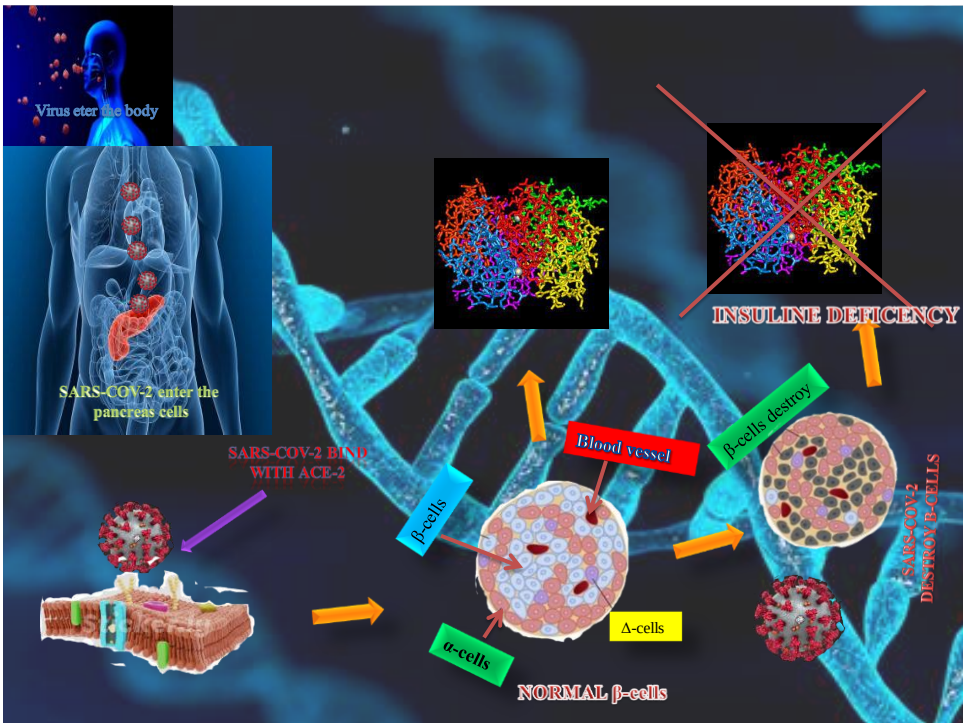

Fig 2 is systematic representation of SARS-COV-2 effect and damage β-cells and resist insulin as result causes diabetes including T1D and T2D.

6. management with patients and Biomarkers:

SARS-COV-2 is causing diabetes and hyper tension. Recently new diagnosed diabetes patients after COVID-19 blood diet management is must be require for this blood nutrients leve management and creat guideline by WHO. According this guideline ≥ 70mmol/L or 2h, plasma glucose is ≥ 1.1 mmol/L (≥ 200 mg/ml) or HbA1c ≥ 48 mmol/mol [56-58].

A biomarker is one of the most important tools for measuring the pharmacodynamic impact, as well as for identifying early signs of therapeutic response and problems related to disease and treatment. In recent years, biomarkers for the COVID-19 pandemic, diabetes, and other sequelae have included CRP, IL-6, PCT, LDH, AST-ALT, coagulation marker D-dimer, and Troponin T. (table 1) [58].

Biomarkers	importance	rerance
CRP	• This test is used to diagnose coronary artery disease. The CPR test is used to assess inflammation in both acute and chronic diseases. • During COVID-19, the CPR test is utilized to detect bacterial and viral infections, as well as inflammatory bowel illness or gut abnormalities.	[16]
IL-6	• IL-6 is a blood test. • This blood test helps to detect the immune response. • IL-6 can be elevated with inflammation, infection, autoimmune disorders, cardiovascular diseases, and cancers.	[17, 18]
LDH	• The LDH test aids in locating and assessing the degree of tissue damage throughout the body. This examination is also used to track the progression of specific disorders. Kidney disease is one of these.	[20, 21]
PCT	• In addition to identifying bacterial origins of signs and symptoms in a very unwell individual during the COVID-19 condition, the procalcitonin test is helpful in detecting sepsis and severe bacterial infections in the early stages and in differentiating between bacterial infections.	[19]
AST–ALT ratio	• Low amounts of ALT and AST are present in blood; a rise in AST levels may suggest liver damage, illness, or muscle injury. • • Phosphatase alkaline (ALP). ALP is an enzyme present in the liver and bone that aids in the breakdown of proteins. • An high AST/ALT ratio is indicative of long-term consequences such as fibrosis and cirrhosis in chronic viral disorders such as chronic viral hepatitis and chronic alcoholism, as well as non-alcoholic fatty liver disease.	[22]
coagulation marker D-dimer	• • A D-dimer test is used to determine whether you have a blood clotting issue such as Deep vein thrombosis (DVT), which is a blood clot deep inside a vein. These clots often affect the lower legs, although they can occur in other regions of the body as well.	[23]
NT-proBNP	• A BNP or NT-proBNP test is often used to diagnose or rule out heart failure.	[24]

	• If you already have heart failure, the test may be performed to determine the severity of the problem. •	
Troponin T	• • This test is used to diagnose a heart attack that has already happened. If you experience chest discomfort and other symptoms of a heart attack, your doctor will prescribe this test. This test is often done twice more during the next 6 to 24 hours.	[22]

Table 1: this table given information of biomarkers.

7. The association of diabetes with SARS-COV-2 infections path physiological mechanisms (fig 3):

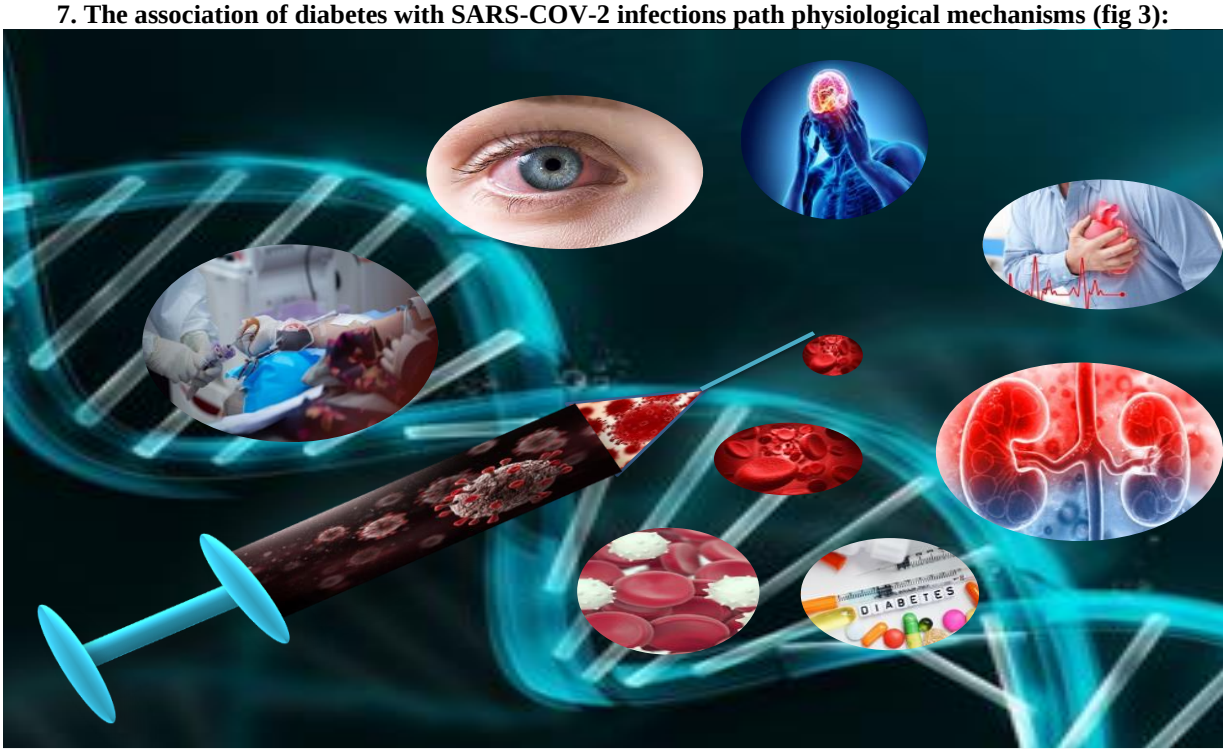

Fig 3 is describe COVID-19 virus is causing some gene mutation disease such as diabetes as well as causing organ failure.

7.1. Immune derangement:

Recently studies thrmobiotics micro-angio pathway (TMA) is pathologically associated with thrombosis in capalires and arteries which leads to microangiopathy hemolytic anemia, thrombocytopenia and organ damage like renal, heart, and neurological disease, and cardiac dysfunction [59]. This TMA is a risk factor for SARS-COV-2 and oxidative stress etc.

Insulin resistance like elevated circulation components C3[35]. Increased C3 level lead to the development of TMA [59-61]. Von Willebrand factor (VWF) is a clotting factor that is required for the pathogenesis of thrombotic thrombocytopenic purpura (TTP), a fatal blood disorder. In hospital studies, outcomes of diabetic patients who have COVID-19 seem TMV-like symptoms.

Immune dysregulation is a significant factor in diabetes patients identified after SARS-COV-2 infection [3]. 107 T1DM patients were investigated by Harsunent et al [62] and Valle et al [63] who found that their total white blood cells (WBC), neutrophil, basophil, and monocyte numbers had reduced. As a consequence, signs of lymphocyte-mid neutrophils were detected. Neutrophilic extracellular trap (NET) is another pathogen-defeating technique. Elastase (NE) and proteinase (PR3), two enzymes that are strongly related to neutrophil enzymatic activity, are what cause NET to develop. Diabetes is being brought on by the transmission of NET that manifests as SARS-COV-2, claim investigations [64-67]. Additionally, the imbalance between TH-17 cells and T cells (trigged cells) causes the blood to become inflamed and produce the cytokines IL-6 and IL-IB. As a result, diabetes is brought on by immunological dysfunction.

Many studies have shown CD4+, and CD28+ cells level is normal to ability trigs to suppress T-cell profication was markedly reduced. SARS-COV-2 infection leads to the down-regulation of CD4+ T-cells and CD8+ T-cells and enhances the production of cytokines CL-6, IL-B, or CXC and leads to T-cell exhaustion, hyper activation of the T-helper (Th) and higher ration of T-cells causes pro-inflammation as result imbalance of differ adaptive immunity.

7.2. Chronic inflammations and oxidative stress:

Chronic inflammation leads due to the dysfunctional function of adipose tissue as a result of decreased synthesis of pro-resolving lipid mediators such as lipoxin.

Chronic diabetes is a kind of long-term diabetes. According to recent research, SARS-COV-2 circulation levels of pro-inflammatory cytokines such as IL-IB, IL-6, IL-7, IL-8, IL-17, IFN, THI-, CXCL-10, and Monocyte chemoattractant protein-1 (MCP-1) enhance ARDS mortality [43, 68]. Increased generation of ROS and AGEs in diabetes patients linked to oxidative stress leads to the creation of the NLRP3 inflammasome and activation of the NF-KB pathway, both of which have a detrimental effect on insulin resistance [69].

Oxidative stress occurs when there is an imbalance between the synthesis of ROS and antioxidants, and it can manifest itself in four different ways (fig 4). These four pathways result in an excess of superoxide molecules, which encourages cell damage and adhesion

molecules. Hyperglycemia patients lead AGE level activation receptor RAGE in the kidney [46]. RAGE leads diabetic pathway. AGE-induced oxidative stress generation and inflammation and fibrotic in a human cultured mesangial cell [4]. This hypoxia is manifest in species, trigged formation free radical which is lead upregulation of pro-inflammation of cytokines radical that in vicious cycle activate macrophages and neutrophils produce free molecules.

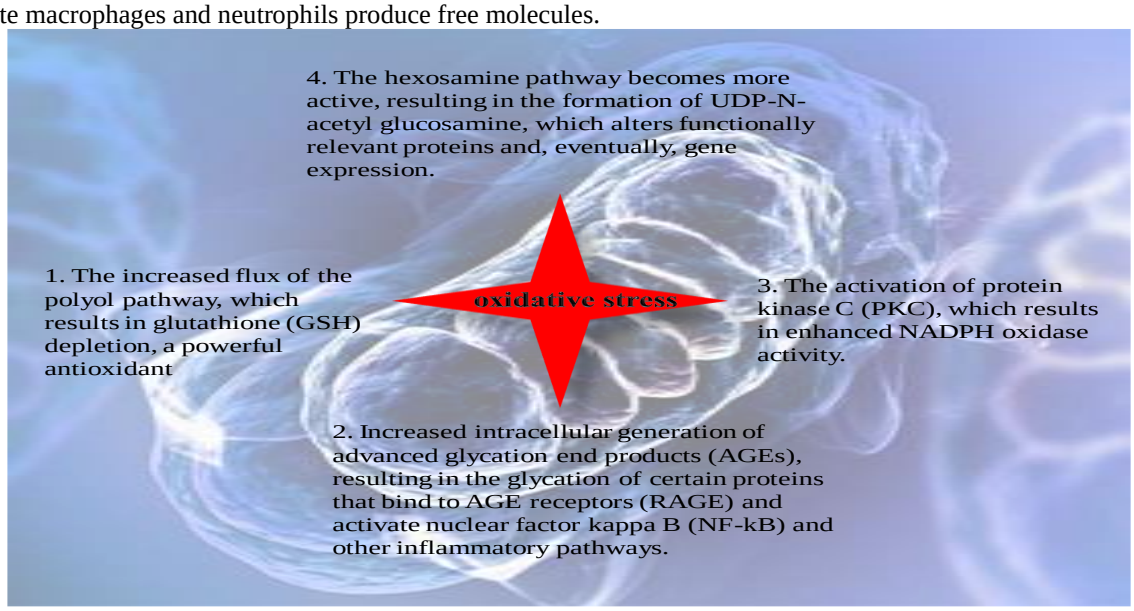

Fig 4 is describe four pathway. These four pathways result in an excess of superoxide molecules, which lead cell damage and adhesion molecules.

The interaction of SARS-COV-2 with ACE-2 enhances Angiotensine-II availability and upregulates (NADPH) oxides (NOx) and ROS generation [98, 99]. ROS causes NOS expression by activating NF-KB, resulting in increased no formation and hypoxia [70, 71].

7.3. chronic endothelial dysfunction:

SARS-COV-2 direct attack on endothelial cells. During the Covid-19 leading disinfection, SARS-COV-2 binds with ACE-2 and causes endothelial dysfunction, inflammation, and pro-inflammation [72-74]. Additionally, inflammatory-mediated derangement and pro-coagulability are contributed by IL-6 or TNF- enhanced vascular permeability, which causes fluid shift and edema in the injured glycocalyx [75]. The pro-inflammatory cytokine that was produced by the infected endothelial cells led to immune-mediated lung damage and tiny pulmonary arteries as well as multi-organ failure and ARDS.

SARS-COV-2 enters the cells by binding with ACE-2 and predominantly expression of airway epithelial cells (ACE) as a result of increased lung injury. Alveolar damage, perivascular T-cell infiltration, and severe endothelial injury linked to the presence of intracellular virus and damaged cell membrane were all seen in several investigations using sample individuals who died from COVID-19. During COVID-19, a pulmonary vessel was present in individuals who had intracellular viruses and mistrusted cell membranes.

8.1. Diabetes leads to neurological complications after SARS-CoV-2 infection

Approximately one-third of COVID-19 patients have been shown to develop neurological symptoms, including headache, disturbed consciousness, paresthesias, brain tissue edema, stroke, neuronal degeneration, and neuronal encephalitis [76].

The blood-brain barrier (BBB), which is made up of endothelial cells, neurons, astrocytic end feet, pericytes, and a thick basement membrane, facilitates communication between the peripheral and the central nervous system (CNS). This BBB permits the movement of different nutrients, ions, glucose, water, amino acids, and hydrophobic molecules, such as O2, CO2, and hormones[116], but it prevents the passage of pathogens, peripheral inflammatory mediators (such as cytokines and antibodies), as well as large or hydrophilic molecules, into the CNS [77].

Diabetes-induced hyperglycemia increases vascular endothelial growth factor (VRG-7) production and activation, as well as capillary development (BBB). SARS-COV-2 expresses the ACE-2 receptor in diabetics, penetrates the brain CNS, stimulates pro-inflammatory cytokine production, produces cytokines Strome in the side CNS, and breaks the blood-brain barrier (BBB).

The pathogenesis of encephalopathy is diabetes dysfunction in the brain it's called diabetes encephalopathy (DE). Electrophysiological, neurochemical, and structural abnormalities are seen in DE, a kind of chronic microvascular function diabetes mellitus (DM) [107, 108]. Some research has linked T1D to autoimmune neurological problems because the antibody against glutamic acid decarboxylase is more prevalent than normal in the body and is a key biomarker for limbic encephalopathy [78].

SARS-CoV-2 may infect brain tissue, causing a variety of pathophysiological symptoms consistent with CNS illness. Research that enrolled 8 COVID-19 patients, for example, discovered an increase in anti-SARS-CoV-2 antibodies in the CSF of comatose or encephalopathic patients, implying intrathecal IgG production or BBB breakdown. BBB breakdown may allow proinflammatory cytokines and inflammatory mediators to enter the CNS, resulting in neuroinflammation and neurodegeneration [78].

Recent studies show that SARS-COV-2 is induced neurological dysfunction. Douad et al [81] studied SARS-COV-2 positive patients' several striking features which are associated with brain dysfunction alterations in the presence of tissue damage biomarkers connected with the primary olfactory cortex and significant reduction of brain size during SARS-COV-2. SARS-COV-2 enters the brain and RNA in olfactory mucosa, its nervous projection, and distinct CNS region [79].

8.2. Diabetes leads to renal disease after SARS-CoV-2 infection

According to the data 37 million people get affected by chronic kidney disease. Diabetes caused kidney disease it's called diabetic kidney disease (DKD) or nephropathy. DKD is associated with several structures changes in the kidney, leading to mesangial expansion thinking of the glomerular and tubular basement membrane glomerular sclerosis that manifests clinical symptoms including blood pressure and reduction of glomerular filtration rate (GFR) and leads to the end stage of the kidney as result causing death [80].

Hyperglycemia patients lead AGE level activation receptor RAGE in the kidney [82]. RAGE leads diabetic pathway. AGE-induced oxidative stress generation and inflammation and fibrotic reaction in human cultured mesangial cells [83].

According to various studies, the plausible mechanisms for DKD patients' renal hemodynamic impairment include inflammation, aberrant glucose metabolism, oxidative stress, and overactive RAAS. Patients with DKD have higher plasma levels of prostaglandin E2, and those with poor glycemic control have higher levels of L-arginine-nitric oxide (NO) , both of which can impede tubuloglomerular function [84, 85]. As a result of defective autoregulation, efferent and consequent glomerular hypertension, and overactivation of RAAS in T2D patients, there is an increased level of ANG-2 in the blood. Renal ET-1 production is increased in T2D patients who have renal fibrosis, podocyte damage, and inflammation. Renal ET-1 is crucial for vasoconstrictors.

Hyperglycemia Osmotic diuresis worsens dehydration and leads to acute renal damage in DKA (AKI). Recent research indicates that SARS-COV-2 causes hypovolemia and AKI in COVID-19 patients. In some studies, COVID-19 patients with AKI are associated with reduced renal blood flow independent of left/ right cardiac dysfunction. Which are reduced renal blood flow reduction of GFR and AKI is the lead end stage of kidney and the last death of CKD or DKD patients.

8.3. Diabetes leads to eyes disease after SARS-CoV-2 infection

Diabetes individuals frequently develop diabetes retinopathy (DR). DR is a country that leads in most cases globally [86]. The pathogens of microangiopathy inflammation and retinal neurodegeneration, in patients with hyperglycemia, have been the subject of several investigations [87]. Several processes, including the metabolic route, the polyol system, the production of ACEs, the PKC pathway, and the hexosamine pathway, were affected by hyperglycemia as a pathogenes that resulted in retinal microvascular dysfunction [87]. Blood-retinal barrier (BRB), capillary infection, and ischemia in DR are all caused by hyperglycemia, which is a risk factor for endothelial dysfunction. Along with ischemia, diabetic patients also have proliferative DR and diabetic macular edema that is caused by increased vascular permeability brought on by the production of VFGF through HIFI and phospholipase A2 activation.

On the other hand, the respiratory system is thought to be the primary site of SARS-COV-2 infection. According to various research, SARS-COV-2 virus infections spread through contaminated conjunctiva and filthy hands. Recently, researchers discovered a direct SARS-COV-2 infection method [88,89]. According to investigations by Menuchin-Lasowski et al. [90], SARS-COV-2 infected patients' retinal organoids produce more inflammatory genes linked to acute COVID-19 and produce less IL-33, CXL-2, and CXL-10. According to certain research, ACE-2 is considerably inhibited and leads to the development of SARS-COV-2 and retinal organoids, respectively.

The patient showed an elevation of IL-6 levels in both eyes as well as in the circulation [91]. Findings from this study suggest that SARS-CoV-2-induced cytokine storm may contribute to the pathogenesis of conjunctivitis and keratoconjunctivitis. Studies showed that diabetes is a risk factor for acute infectious conjunctivitis [92].

9. Drug therapy for diabetes patient association with COVID-19.

Fig-4 is describe different medication use for COVID-19 associated diabetes patients.

Researchers have discovered a successful therapy for both types of diabetes, including T1D and T2D. Numerous studies have demonstrated that insulin induction is a successful method of managing diabetes. Table 1and fig lists many medications, including metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone, SGLT2 inhibitors, PPARS, DPP4 inhibitors, and insulin treatment (fig 4). Which are beneficial for the current COVID-19 scenario and effective for the treatment of diabetes.

• Name of the drug	• Mechanism and effectiveness	referance
• 1. metformin	• Metformin antibiotics are used as a treatment for T2D patients and also used for lactic acidosis and sometimes used for lactic acidosis patients who suffer from renal disease. Currently,	[93, 94]

	metformin drug used for COVID-19 symptoms and symptoms in hospitalized patients. • Metformin drugs inhibit the entry of viruses in the cells through the activation of protease and adenosine monophosphate (AMP) and target rapamycin for singing the pathway. • Metformin is an effective treatment for COVID-19-associated T2D patients.	
• 2. sulfonylureas	• Sulfonylureas are oral medications that are used to lower blood glucose levels. • The use of hydroxychloroquine in the production of sulfonylureas may raise the risk of hypoglycemia.	[95]
• 3. Dipeptidyl peptidase-4 (DPP-4)	• DPP Inhibitors use for mainly T2D and currently use for COVID-19 patients • DDP-4 has reduced blood glucose and binds with COVID-19 bind receptors and mitigates their effects.	[96, 97, 98]
• 4. Glucose like peptide-1 (GLP-1)	• GLP-1 is used weakly two times. GLP-1 is an effective treatment for poor blood flow, although it causes weight loss and an increased risk of aspiration pneumonia and dehydration. • This medication reduces the pulmonary T2D immune cytokine response and the degree of lung damage in mice following viral infection. This medicine has a powerful anti-inflammatory impact on the lungs and is now utilized for COVID-19 patients to improve survival rates.	[99, 100]
• pioglitazone	• Patients with type 2 diabetes are prescribed politazone. Typically, metformin, sulfonylurea, and insulin are used with this medication. The doctor suggested diet and exercise after using this medication. However, those with newly discovered diabetes following COVID-19 are more susceptible to the cytokine storm. The medicine pioglitazone reduces the production of cytokines Strome and prevents the release of pro-inflammatory cytokines.	[101-104]
• Sodium glucose xo transporter-2 (SGLT-2)	• SGLT-2 benefits organ protection. This medication helps manage diabetes. SGLT-2 Inhibitors are now being utilised by diabetic individuals who have COVID-19, according to research. Organ failure brought on by COVID-19 ultimately results in death. Clinical results indicate that SGLT-2 medication is beneficial for organ failure patients and that taking it boosts the survival rate of COVID-19 and organ failure patients.	[105, 106]
• Insulin therapy	• The most effective therapy for diabetic people with COVID-19 is insulin. The insulin goal range is 7.8-10.0 mmol/L, and basal insulin and bolus plus insulin correlations must be successful in non-critically sick patients, according to American Diabetes Association recommendations. • The blood glucose levels of inflammation indicators including C-reactive protein (CRP) and mannose-binding levels are decreased by this insulin treatment, which has anti-inflammatory properties. • Patients should not be severely evaluated, according the recommendations. By employing this method, the exposure of COVID-19 patients is reduced by the combination of basal insulin and GLP-1 agonists administered as a single injection. This insulin has a glucose-lowering impact and may have an anti-inflammatory effect when used with GLP-1 agonists.	[107-111]

Table 2 is describing different antibiotics and insulin therapy. Were the uses good outcomes

10. Discussion

COVID-19 is prevalent across the planet. According to the present study, the SARS-COV-2 virus causes type 1 and type 2 diabetes, as well as other diseases and organ failures such as hypertension, dyslipidemia, cardiovascular disease, and renal disease, all of which raise mortality and morbidity rates. During the SARS-COV-2 pandemic, diabetes posed a significant problem for physicians to address.

SARS-COV-2 entering the body Frist binds with ACE-2 and transmembrane serine proteases-2 receptors and enters the cells. SARS-COV-2 expressed some key metabolic organs and tissue such as pancreatic b-cells, adipose tissue, the small intestine, and the kidney [112-114]. However, in this review article, we focus on SARS-COV-2-caused diabetes.

SARS-COV-2 is the primary cause of Type 1 Diabetes, while additional risk factors include Cocsakievirus B, rotavirus, mumps virus, and cytomegalovirus [115, 116]. SARS-COV-2 and hepatitis C, on the other hand, are risk factors for type 2 diabetes.

SARS-COV-2 reaches the pancreatic cells via binding to ACE-2 inhibitors on their surface, damaging b-cells as a result of insulin resistance, and developing type 1 and type 2 diabetes. Recent research indicates that SARS-COV-2-linked hyperglycemia patients have decreased neutrophil activity and increased pro-inflammatory cytokine concentrations, which result in IL-6 and tumor necrosis factor-alpha [117]. Patients with type 2 diabetes, however, got care through COVID-19 This particular patient's upregulation of cytokines and TNR-a function led to the malfunctioning of b cells and the development of insulin resistance.

Biomarkers are useful for identifying information regarding COVID-19 individuals with diabetes. CRP, IL-6, PCT, LDH, AST-ALT, coagulation marker D-dimer, NT-proBNP, and Troponin T were reported for COVID-19-associated patients according to the recommendations.

Diabetes patients who had just been diagnosed underwent COVID-19. This patient group has trouble controlling their blood sugar levels. Use some medications and treatments for COVID-19-associated diabetic patients to achieve this goal. Metformin, sulfonylureas, DDP-4, GLP-1, and insulin treatment were recently used. Better results have been shown and patient mortality and morbidity have increased when this medication and therapy have been used for COVID-19-associated diabetic patients.

11. Conclusion:

COVID-19 has a global impact, increasing death and morbidity. SARS-COV-2 has recently been studied in two or three waves between 2021 and 2022, causing diabetes, other disorders, and organ failure. According to the guidelines, biomarkers can help identify successful treatments. Because no specific drug or vaccination were available for COVID-19 first to second waves, individuals with newly diagnosed diabetes received old therapy.

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