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REVIEW

Diabetes as one of the long-term COVID-19 complications: from the potential reason of more diabetic patients' susceptibility to COVID-19 to the possible caution of future global diabetes tsunami

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Abstract

According to recent researches, people with diabetes mellitus (type 1 and 2) have a higher incidence of coronavirus disease 2019 (COVID-19), which is caused by a SARS-CoV-2 infection. In this regard, COVID-19 may make diabetic patients more sensitive to hyperglycemia by modifying the immunological and inflammatory responses and increasing reactive oxygen species (ROS) predisposing the patients to severe COVID-19 and potentially lethal results. Actually, in addition to COVID-19, diabetic patients have been demonstrated to have abnormally high levels of inflammatory cytokines, increased virus entrance, and decreased immune response. On the other hand, during the severe stage of COVID-19, the SARS-CoV-2-infected patients have lymphopenia and inflammatory cytokine storms that cause damage to several body organs such as β cells of the pancreas which may make them as future diabetic candidates. In this line, the nuclear factor kappa B (NF-κB) pathway, which is activated by a number of mediators, plays a substantial part in cytokine storms through various pathways. In this pathway, some polymorphisms also make the individuals more competent to diabetes via infection with SARS-CoV-2. On the other hand, during hospitalization of SARS-CoV-2-infected patients, the use of some drugs may unintentionally lead to diabetes in the future via increasing inflammation and stress oxidative. Thus, in this review, we will first explain why diabetic patients are more susceptible to COVID-19. Second, we will warn about a future global diabetes tsunami via the SARS-CoV-2 as one of its long-term complications.

Keywords SARS-CoV-2 · COVID-19 · Diabetes · Lymphopenia · Stress oxidative · NF-κB pathway

Abbreviations

COVID-19	Coronavirus disease 2019
ROS	Reactive oxygen species
NF-κB	Nuclear factor kappa B
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
RBD	Receptor-binding domain
ACE2	Angiotensin-converting-enzyme 2
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor-α
IFN	Interferon
PGC1α	PPARγ coactivator 1α
GLUT	Glucose transporter
MAPK	Mitogen-activated protein kinase
JAK/STAT	Janus kinases/signal transducers and activators of transcription
SOCS	Suppressor of cytokine signaling
JNK	C-jun N-terminal kinase
IR	Insulin resistance
GLP1	Glucagon-like peptide 1
PPARγ	Peroxisome proliferator-activated receptor-γ
PI3K	Phosphatidylinositol-3 kinase
SGLT2	Sodium–glucose cotransporter 2

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Introduction

Diabetes prevalence is a major public health concern and is rapidly increasing worldwide (Esakandari et al. 2020; Ghaffari et al. 2023). According to estimates, the prevalence of diabetes among people aged 20–79 worldwide in 2021 will be 10.5 percent (536.6 million), rising to 12.2 percent (783.2 million) in 2045 (Nabi-Afjadi et al. 2021; Sun et al. 2022). This disease has serious side effects, including atherosclerosis, neuropathy, nephropathy, retinopathy, and cause high morbidity and mortality as well (Fadaei et al. 2020; Khomari et al. 2021).

Among several factors resulting diabetes, such as genetics and life style, various viruses have also been associated with diabetes, including respiratory viruses, rotavirus (Honeyman et al. 2000, 1998), mumps virus (Hyöty et al. 1988), cytomegalovirus (Pak et al. 1988), Rubella (Forrest et al. 1971; Menser et al. 1978), hepatitis C virus (HCV) (Czaja et al. 1995) and Coxsackie virus B (CVB) (Hyöty & Taylor 2002). Respiratory virus infections, such as those caused by the s respiratory syncytial virus (RSV) (Swapna et al. 2022), the middle east respiratory syndrome coronavirus (MERS-CoV) (J.-K. Yang et al. 2010), and the severe acute respiratory syndrome coronavirus (SARS-CoV) (Badawi & Ryoo 2016) also lead to insulin resistance which is the hallmark of Type 2 diabetes mellitus (T2DM) (Swapna et al. 2022).

Due to zoonotic transmission and some common clinical characteristics, the recent outbreak of coronavirus disease 2019 (COVID-19) is similar to SARS-CoV (2002–2003) in China and the MERS-COV (2012) in Saudi Arabia as well (Hui, Memish, and Zumla, 2014). Phylogenetic analysis of the receptor-binding domain (RBD) of the betacoronavirus lineage suggests that 2019-nCoV is closely related to two bat-derived SARS-like coronaviruses (bat-SL-CoVZC45 and bat-SL-CoVZXC21) with 88–89% similarity, whereas its similarity is 50 and 79% to the SARS-CoV and MERS-CoV, respectively (Lai et al. 2020).

The SARS-CoV-2, the focus of this review study, is a type of SARS-CoV that emerged in 2019, enters the lung cells through binding of the spike (S) protein to angiotensin-converting-enzyme 2 (ACE2) on the host cells. It has been shown that ACE2 is the receptor of SARS-CoV-2 which allows virus to enter the host cells (W. Li et al. 2003; Zalpoor et al. 2022a, b, c, d, e; Zalpoor, Shapourian, Akbari, Shahveh, and Haghshenas, 2022). It has been revealed that the binding affinity of the spike glycoprotein of SARS-CoV-2 to ACE2 receptor is 10–20 times higher than that of the SARS-CoV (Payandeh et al. 2021; Wrapp et al. 2020). Briefly, the tip of ACE2's subdomain I is where the spike glycoprotein's RBD attaches (F. Li et al. 2005; W. Li et al. 2003; Wrapp et al. 2020). After binding, the viral membrane fuses with the host cell membrane, viral RNA is released into the cytoplasm, and infection is established. Similar to the lung cells, the SARS-CoV-2 enters pancreatic islet cells using ACE2 and damages them causing acute diabetes (J.-K. Yang et al. 2010). Subsequently, SARS-CoV-2 infection alters the immune system, resulting in deregulation of the immune system and increased expression of inflammatory pathways, particularly nuclear factor kappa B (NF-κB), that induces additional production of pro-inflammatory cytokines like IL-6 and consequently, cytokine storms through various mechanisms (X. Li et al. 2020; McGonagle et al. 2020; Zalpoor et al. 2022a, b, c, d, e; Zalpoor et al. 2022a, b, c, d, e; Zalpoor, Aziziyan, et al., 2022). Moreover, based on findings, oxidative stress is a significant risk factor during COVID-19 (Mohiuddin and Kasahara 2021). During COVID-19, intracellular zinc deficiency degrades zinc-dependent antioxidant proteins such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), resulting in an excess of reactive oxygen species (ROS) production, and further deterioration of oxidative stress (Scheinberg et al. 2021). This condition can damage the pancreatic cells particularly β cells producing/releasing insulin. It should be noted that these hyper activated pathways of inflammation and stress oxidative have been demonstrated in diabetic patients. During COVID-19, more activation of inflammation and stress oxidative pathways possibly is one of the reasons that the diabetic patients are more vulnerable to SARS-CoV-2.

In this line, epidemiologic studies have revealed an association between inflammatory biomarkers and elevated oxidative stress, and the occurrence of diabetes and its complications. The inflammatory response probably plays a role in the development of diabetes by causing insulin resistance, which in turn is enhanced in the presence of hyperglycemia, promoting long-term complications of diabetes (Lontchi-Yimagou et al. 2013). It has been shown that diabetic patients have high levels of inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) (Hu et al. 2004; Lechleitner, Herold, Dzien-Bischinger, Hoppichler, and Dzien, 2002; Pradhan et al. 2001), IL-1β (Eizirik & Mandrup-Poulsen 2001), IFN-γ (Kartika et al. 2020), and NF-κB (X. Li et al. 2020; McGonagle et al. 2020). Moreover, clinical studies have demonstrated that COVID-19 patients with diabetes without other comorbidities had higher serum levels of inflammation-related biomarkers such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor (TNF) (G. Chen et al. 2020a, 2020b; Giamarellos-Bourboulis et al. 2020; Huang et al. 2020; Lucas et al. 2020; Zhou et al. 2020) and were susceptible to the cytokine storm, leading to the rapid exacerbation of COVID-19.

Therefore, these inflammatory cytokines can results in structural and functional abnormalities like insulin resistance, insufficient insulin secretion, and eventually a rise in blood glucose levels (Nicholls et al. 2003). It has been found that the expression of pro-inflammatory and anti-inflammatory cytokines may be severed by single nucleotide polymorphisms (SNPs) in the regulatory genes (15, 16). It has been shown the association of IL-6, IL-10, and TNF-α gene polymorphisms with metabolic diseases (Boraska et al. 2010b; Bouhaha et al. 2010; Erdogan et al. 2012; Saxena et al. 2013b; Vozarova et al. 2003b; Zeggini et al. 2005a). So, the effects of inflammatory mediators, cytokine storm, and oxidative stress in COVID-19 and the pathogenesis of diabetes have provided the insight that there will be a tsunami of COVID-19-induced diabetes and further complications, higher morbidity and mortality in the future (Fig. 1).

COVID-19 infection reduces the number of ACE2 receptors and inducing their endocytosis, which releases RAS inhibition and further reduces ACE2 expression. The cytokine storm caused by the COVID-19 infection's hyper-inflammation also produces pro-inflammatory cytokines. The cytokine storm and immune cell imbalance will cause systemic organ dysfunction in addition to harming cardiac tissue and β-cells.

Association between diabetes and inflammation/oxidative stress

The frequency of diabetes is increasing rapidly worldwide and has become a major public disease (Pouriamehr et al. 2019; Safizadeh et al. 2020; Whiting et al. 2011). Despite tremendous efforts to extend the lives of diabetic patients, diabetes remains the fifth leading cause of death overall (about 1.6 million death) (Roglic et al. 2005). Oxidative stress has been reported as one of the known reasons for the pathogenesis of diabetic complications (Giacco and Brownlee 2010). Increased insulin, free fatty acid, and/or glucose levels may increase ROS production and oxidative stress, activating stress-sensitive signaling pathways (Evans et al. 2003). Diabetic metabolic disorders cause mitochondrial superoxide overproduction in both large and small vessel endothelial cells and myocardium. (Giacco and Brownlee 2010). In fact, the oxidative capacity of skeletal muscle, which underlies mitochondrial capacity, directly corresponds to insulin sensitivity (Simoneau and Kelley 1997), and decreased mitochondrial oxidative phosphorylation is related to insulin resistance (Petersen et al. 2004). Decreased numbers and altered morphology of mitochondria have been observed in skeletal muscle of patients with type 2 diabetes (Kelley et al. 2002). Nuclear respiratory factor 1 (NRF1) and PPARγ coactivator 1 α (PGC1 α), two genes that control mitochondrial biogenesis,

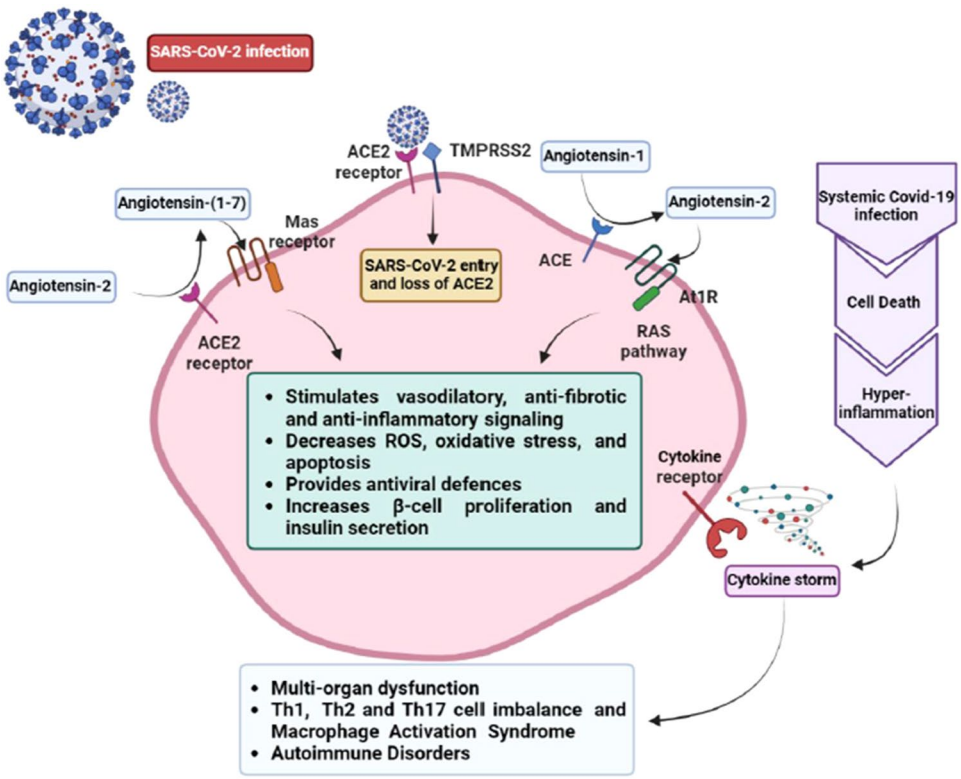

Fig. 1 COVID-19 pathogenesis in diabetic patients. The ACE receptor converts angiotensin-1 into angiotensin-2, causing affecting RAS signaling and promoting systemic oxidative stress and apoptosis. This reduces β-cells proliferation and insulin secretion while increasing the risk of cardiovascular problems. The ACE2 receptor protects β-cells by converting angiotensin-2 to angiotensin-(1–7), which stimulates vasodilatory, anti-inflammatory, and anti-fibrotic signaling, reduces oxidative stress, increases β-cell proliferation, provides antiviral defenses and, secretes more insulin via the Mas receptor

may have decreased expression as a result of these changes (Sparks et al. 2005). Recent studies have stated that ROS damage directly contributes to the development of many chronic diseases, such as insulin resistance and the pathogenesis of type 2 diabetes (Hurrle & Hsu 2017). NADPH oxidase 4 (NOX4) is a powerful oxidase that generates ROS (Campa et al. 2015). The retromer is activated by increased ROS, which in turn activates casein kinase-2 (CK2) (Ma et al. 2014). The retromer then sends downstream signals in the trans-Golgi network, directing the transport of GLUT4 to the lysosomes for degradation as opposed to the plasma membrane. As a result, the oxidative environment maintains elevated intravascular glucose levels. Because of environments high in nutrients, mitochondria also accord to the oxidation that takes place in the cell. Consequently, in hyperglycemia, the mitochondria are hyperactive and produce more of their natural byproduct, ROS. (Henriksen et al. 2011). The mitochondria that are in charge of producing ROS directly stimulate NF-kB (Cooper, Hausman, and Hausman, 2007), JNK (Tsai et al. 2012), and p38 mitogen-activated protein kinase (MAPK) (Al-Lahham et al. 2016), which in turn causes mitochondria-induced stress responses. As a result, the infrastructure of the cell is damaged. Additionally, elevated ROS levels cause mitochondrial fission, which affects the insulin receptor pathway and stress proteins linked to insulin resistance in skeletal muscle (Boucher et al. 2014) (Jheng et al. 2012).

Additionally, diabetic patients overproduced RONS and had the highest activity levels of superoxide dismutase (SOD) in their erythrocytes (Cleeman, Grundy, Becker, and Clark, 2001). Oxidative stress would occur in the absence or ineffectiveness of RONS defenses, resulting in the activation of cellular stress response mechanisms like NF-kB, p38MAPK, and JNK/SAPK. These mechanisms would stimulate the production of inflammatory cytokines, which would have an impact on diabetic complications and pancreatic beta cell dysfunction, intensifying defective insulin production (Evans et al. 2002). Increased p38MAPK signaling in diabetes has been linked to late complications like ROS-mediated neuropathy (73) and nephropathy in both forms of the disease (Price et al. 2004) (Bahreini et al. 2021; Komers et al. 2007). One of the components of the activator protein (AP)-1 transcription factor is the transcription factor c-jun, which is bound to and phosphorylated by activated JNK/SAPKs. A positive feedback loop is created when JNK/SAPKs transactivate c-jun by increasing the expression of AP-1 related genes, such as c-jun (Dalton et al. 1999). Numerous studies have been conducted on AP-1's redox regulation, which set out a model for other transcription factors redox regulation like NF-κB (Suyama et al. 2001). Taken together, the p38 MAPK, JNK/SAPK, and NF-κB pathways are potential stress-sensitive signaling systems that can chronically results in the late diabetes complications (Evans et al. 2002).

Additionally, it is thought that infiltrating macrophages secrete inflammatory cytokines as a consequence of hyperglycemic-induced oxidative stress, which results in both local and systemic inflammation (Wellen & Hotamisligil 2005). High glucose concentrations are thought to trigger the release of inflammatory mediators, which are thought to be mediated by oxidative stress (Gumieniczek et al. 2005). Consequently, the pathophysiology of diabetes mellitus has been linked to chronic inflammation and oxidative stress. In physiological and pathological states, oxidative stress and inflammation are inseparable (Ambade and Mandrekar 2012). IL-6 (a single chain protein) is created by fibroblasts, monocytes, T cells, B cells, and other cell types (Nishimoto and Kishimoto 2006; Seif et al. 2023; Van Snick 1990). IL-6 affects the change from acute to chronic inflammation (Cronstein 2007). IL-6 is one of the main pro-inflammatory cytokines that is unequivocally associated with the improvement of insulin resistance and T2DM through the contribution of different pathways (Bastard et al. 2006). It mediates the release of additional cytokines that enhance the inflammatory response and regulates or stimulates the production of chemotactic mediators, cell adhesion molecules, and other cytokines (Fisman and Tenenbaum 2010; Kamimura, Ishihara, and Hirano, 2003). On the other hand, IL-6 receptors (IL-6R) are linked to the JAK/STAT pathway family of cytokine class I receptors (Bastard et al. 2006; Ebrahimi et al. 2022; Fahmideh et al. 2022). It initiates intracellular signaling pathways by binding to IL-6R (known as a type I cytokine receptor). IL-6 and IL-6 R interacts to forms a heterodimer with gp130 (Taga et al. 1989). The formed complex activates the JAK/STAT pathway in IL-6 target cells (Heinrich et al. 1998). Clearly, insulin signaling pathways and IL-6 interact strongly that normally prompts a hindered organic impact of insulin (Bastard et al. 2006). Through its negative feedback control, STAT proteins activate IL-6 and cause suppressors of cytokine signaling proteins (SOCS) to be expressed (Endo et al. 1997; Naka et al. 1997; Starr et al. 1997) (Shi et al. 2006; Ueki et al. 2005, 2004). In the study, C/G polymorphisms in the IL-6 gene were found to be associated with a significant increase in the risk of T2DM. An insulin sensitivity polymorphism at position 174 (G > C) is also promoted by IL-6 (Testa et al. 2006).

In addition, it has been demonstrated that individuals who have clinically diagnosed diabetes with insulin resistance have elevated levels of the tumor necrosis factor (TNF-α) (Alexandraki et al. 2006). During acute inflammation, macrophages and monocytes produce the inflammatory cytokine TNF-α, which is responsible for a

variety of cell-to-cell signaling events that cause necrosis or apoptosis (Idriss and Naismith 2000). By activating the NF-κB transcriptional factor, which is an important modulator of pancreatic cell death, TNF-α induces apoptosis in -cells of pancreatic islets. Phosphorylation of insulin receptor substrate-1 (IRS-1) (at serine residue) is triggered by TNF-α activation, which plays an inhibitory role for insulin receptor and prevents phosphatidylinositol-3 kinase activation signaling. Downregulation of IRS-1, perilipin, CEBP-PPAR, GLUT4, and Acrp30 protein levels is another way that TNF-α can affect insulin sensitivity in adipose tissues (Akash et al. 2018). A polymorphism at 308 G/A (rs1800629) has also been shown to develop insulin resistance and the transcriptional activity of TNF-α (Das et al. 2006; Golshani et al. 2015). Additionally, the 238 G/A (rs361525) polymorphism has been linked to the onset of T2DM in the Mexican population (Guzmán-Flores et al. 2011). The activation of TNF-α also stimulates transcription factors, such as NF-κB. The induction of the expression of genes related to the signal regulation and inflammation is facilitated by these transcription factors. (Akash et al. 2018). The NF-κB can translocate to the nucleus, where it controls how inflammatory proteins like IL-6, IL-1, and interferon- β are expressed (Evans et al. 2002; Libermann and Baltimore 1990) and increases the number of genes that make inflammatory mediators like TNF-α and IL-6 (Collart et al. 1990; Hoffmann and Baltimore 2006; Shakhov et al. 1990).

Additionally, apoptosis and impairment of β-cell function are caused when insulin-secreting pancreatic β cells are exposed to IL-1 solely or in combination with interferon IFN -γ and/or TNF-α (Eizirik and Mandrup-Poulsen 2001). A stress-activated member of the mitogen-activated protein kinase (MAPK) family of threonine/serine kinases involved in the transmission of stress and apoptotic signaling in many cells, the c-jun N-terminal kinase (JNK) pathway is activated by IL-1 β in β-cells (Major & Wolf 2001; Miyauchi et al. 2009; Welsh 1996). Specific MAPK, MKK4 and MKK7, dual phosphorylate Thr183 and Tyr185 to activate JNK, which in turn is activated by a MAPK. (Chang & Karin 2001; Davis 2000). Therefore, cytokine-induced β -cell apoptosis requires the JNK. (Ammendrup et al. 2000; Bonny et al. 2001, 2000). By inducing STAT1 phosphorylation in macrophages under hyperglycemia, it is said that IFN-γ associated to the pathogenesis of T2DM through increasing the MHC class I and II and adhesion molecules expression on various cell types, including β islets of the pancreas. Phosphorylated STAT1 translocate to the nucleus, where it causes several pro-inflammatory genes, like MMP1, to be activated. (Kartika et al. 2020). It has been demonstrated that polymorphisms in the + 874 region of the IFN-γ gene are associated with type 2 diabetes, and that diabetic patients in Greece's provinces have a higher frequency of the AA allele (Tsiavou et al. 2005).

Association between COVID-19 and inflammation/stress oxidative in diabetes-competent individuals or diabetic patients

With the explanations mentioned above, it would be understood why diabetic patients were one of the most susceptible groups during the COVID-19 pandemic. Diabetes mellitus incidence was shown to be 58 and 33% in COVID-19 patients hospitalized in ICUs in the USA, suggesting a connection between severe COVID-19 and diabetes mellitus. According to the study conducted in the UK, patients with T1DM had a higher mortality rate than people without T1DM. Patients with T1DM were older and had higher HbA1c levels, impaired renal function, arterial hypertension, and cardiovascular events. These findings confirm the link between T1DM and inadequate COVID-19 results (Barron et al. 2020; Holman et al. 2020). It is known that a number of processes contribute to the clinical severity of COVID-19 being increased in people with diabetes mellitus (Fig. 2) (Tang et al. 2020). On the other hand, according to several pieces of evidence that will be discussed in the following it can be concluded that SARS-CoV-2-induced stress oxidative and inflammation in pancreatic island cells can make peoples susceptible or competent to diabetes. Insulin resistance, a hallmark of T2DM, has been linked to RSV (Swapna et al. 2022), SARS-CoV (J.-K. Yang et al. 2010), and MERS-CoV (Badawi and Ryoo 2016; Nabi-Afjadi et al. 2022). SARS-CoV-2, a novel coronavirus, quickly spread throughout the world, triggering a global health emergency (Horton 2020). Those who are older and/or have comorbid conditions like diabetes mellitus, hypertension, obesity, and chronic kidney disease are more infected/susceptible to SARS-CoV-2 (Cure and Cure 2020). An essential regulator of the renin–angiotensin–aldosterone system (RAAS) is the ACE2 enzyme, which acts as a functional receptor on the surfaces of the host cell for the entry of SARS-CoV-2. (Beyerstedt et al. 2021).Systemic vascular resistance and blood volume are crucially regulated by RAAS. It contains three major mixtures: aldosterone, renin, and angiotensin II. They respond to lowered renal blood pressure by increasing arterial pressure. The body is able to sustainably raise blood pressure through these mechanisms (Hall, do Carmo, da Silva, Wang, and Hall 2019; Jie Liu et al. 2019). COVID-19 progresses when SARS-CoV-2 activates RAAS, particularly in comorbid patients (Beyerstedt et al. 2021). It has been reported that diabetes increases the expression of ACE2 in the bloodstream (Roca-Ho et al. 2017) in both T1DM

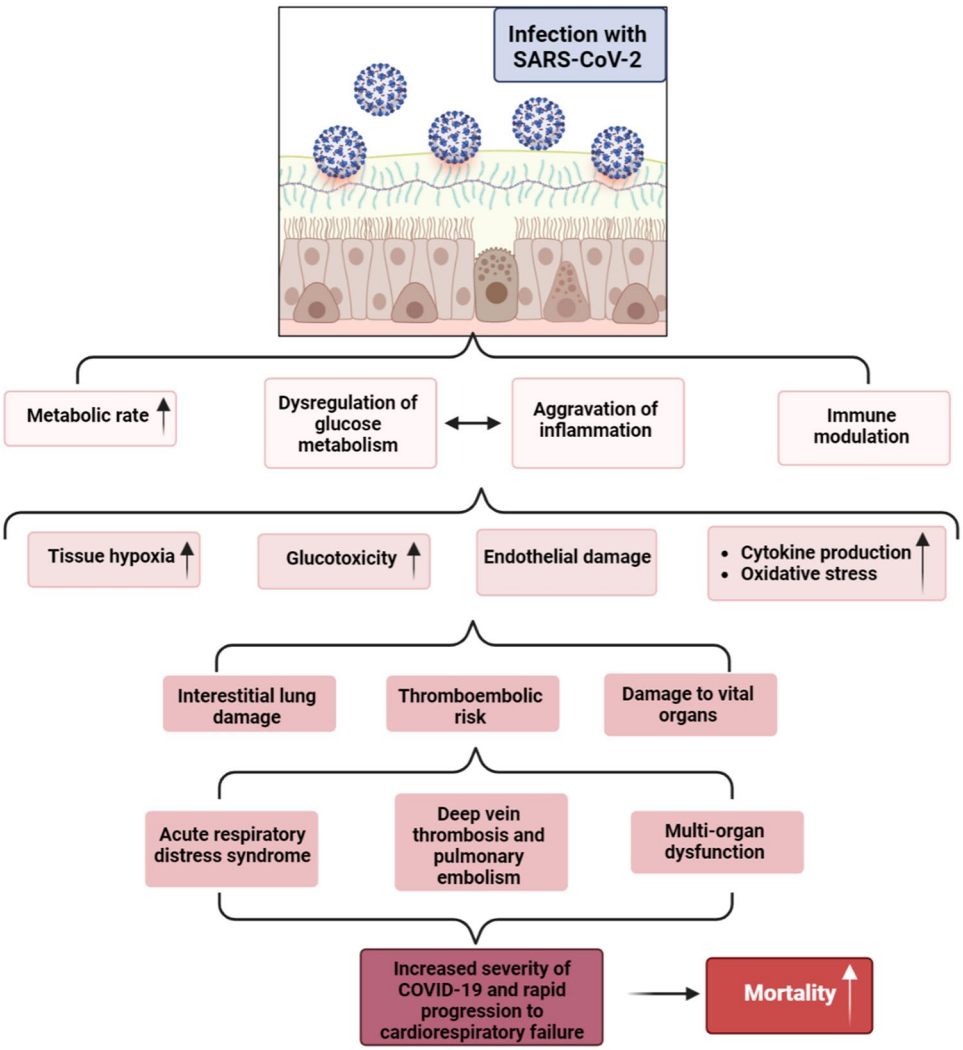

Fig. 2 Clinical processes that may enhance in patients with diabetes mellitus following SARS-CoV-2 infection

(Burns et al. 2017) and T2DM (Gutta et al. 2018). Also, increased levels of ACE2 protein have been reported in the lung, heart, kidney, and pancreas of nonobese diabetic mice (Roca-Ho et al. 2017). When insulin was administered, the elevated levels of ACE2 protein in the diabetic mice's lungs returned to normal, demonstrating the primary impact of hyperglycemia on ACE2 protein levels (Roca-Ho et al. 2017). So, diabetic patients may be more likely to contract SARS-CoV-2 due to higher levels of ACE2 mRNA in the lungs (Fang et al. 2020). The ACE2 and ACE share 42% of their amino acid sequence in their catalytic domain. However, there are numerous differences between the two enzymes. Intriguing findings include the upregulation of ACE2 and downregulation of ACE in renal cortical tubules. It is possible that the high flow occurs during hyperglycemia is linked to local downregulation of the renin-ANG system. Through the activation of Na + /H + exchange, the ANG II encourages sodium reabsorption (Moe, Alpern, and Henrich 1993; O. W. Moe et al. 1993a, b; Valles et al. 2005). Thus, it is possible to consider the renal cortical tubular downregulation and upregulation of ACE2 as a potential means of reducing ANG II overactivity. ANG II-driven sodium reabsorption caused by hyperglycemia would be reduced in this manner, leading to sodium and water diuresis (Soler et al. 2009).

The occurrence of T2DM and complications is also associated with inflammatory biomarkers (Lontchi-Yimagou et al. 2013). There is growing evidence that chronic activation of pro-inflammatory pathways in insulin-target cells may contribute to obesity, insulin resistance, and related disorders, such as T2DM (Shoelson 2006). Moreover, some inflammatory cytokine gene polymorphisms have been reported as a risk factor for diabetes that needs to a stimulator such as SARS-CoV-2 infection (Boraska et al. 2010a; Bouhaha et al. 2010; Erdogan et al. 2012; Heijmans et al. 2002; Saxena et al. 2013a; Vozarova et al. 2003a; Zeggini et al. 2005b). For example, COVID19 risk has been linked to genetic variations in a number of inflammatory cytokines, including TNF-α (rs1800629), IFNAR2 (rs2236757), IFNB (rs2071430), IFNG (rs2430561), IL4

(rs2070874), and IL1RN (rs315952) (Paim et al. 2021; Saleh et al. 2022). On the other hand, a polymorphic variation in the IL-6 gene may increases the risk for T2DM development (Illig et al. 2004; Saxena et al. 2014; Vozarova et al. 2003a). In several groups, the TNF-α 308 G/A gene variant was also targeted in T2DM. In Arragonians, T2DM was found to be linked to the TNF-α 308 G/A gene variant (Vendrell et al. 2003). These finding reveal the correlation of COVID-19 and diabetes.

In terms of the upregulation of ACE2 expression in the lungs, diabetes is causally associated with increased susceptibility to the new coronavirus (Deng et al. 2021). Diabetes caused by a virus infection may result from virus-associated β-cell destruction. It appears that SARS-CoV-2 impairs glucose homeostasis in humans (Müller et al. 2021). The study revealed that SARS-CoV-2 infects both exocrine and endocrine pancreatic cells. In this regard, SARS-CoV-2 infects and replicates in cultured human islets and expresses viral entry proteins in human β-cells. This condition is associated with morphological, transcriptional, and functional changes, such as decreased numbers of granules that secrete insulin when glucose is present and impaired insulin secretion due to glucose withdrawal (Müller et al. 2021). On the other hand, the severity of COVID-19 leads to patients developing respiratory distress syndrome (ARDS) and multiple organ dysfunction with a high death rate. There is a possibility that this is related to the "cytokine storm," an inflammatory state caused by massive cytokines released by macrophages and monocytes infected with SARS-CoV-2, triggering a cascade of damage involving several organs (Iwasaki et al. 2021).

During the innate immune response to a viral infection, pattern recognition receptors (PRRs) recognize virus-specific molecular structures known as pathogen-associated molecular patterns (PAMPs). The binding of PAMPs to PRRs initiates the inflammatory response, signaling pathways and induce expression of pro-inflammatory cytokines through activation of the transcription factors like NF-κB, activation protein 1, and interferon response factors three and seven. These activated factors induce expression of the inflammatory cytokines, chemokines, and adhesion molecules as well (Thompson & Kaminski). The intracellular RAS is involved in signaling pathways; Angiotensin 2 (Ang2), which is derived from Angiotensin 1 with the aid of ACE, induces the production of ROS and NF-κB through Angiotensin Type1 Receptor (AT1R) and the phosphatidylinositol-four, five-bisphosphate three-kinase/protein kinase B (PI3K/Akt) pathway, increasing pro-inflammatory cytokines inclusive of IL-6, chemokines, and adhesion molecules in tissue-resident cells within the amplifying inflammatory cycle (Fyhrquist and Saijonmaa 2008). Thus, people with high ACE2 expression level are more likely to broaden a storm of IL-6-primarily based inflammatory factors (Okabayashi et al. 2006).

Specifically, IL-6 is secreted by immune cells, including B and T lymphocytes, macrophages, dendritic cells, monocytes, mast cells, and many non-lymphocytes, including fibroblasts and endothelial cells. Factors like TNF-α and TLRs particularly associated with the secretion and activation of IL-6 (Jones and Jenkins 2018). The risk of developing COVID-19 in the Turkish population was significantly correlated with the IL-6 polymorphism at position 174 G/C (rs1800795), according to a recent study (Kerget and Kerget 2021). Literature reviews suggest that IL-6 signaling is mediated through binding to the α-interleukin-6 receptor (α-IL-6R), which in turn complicates activation of the β-receptor gp13 dimerization (Wolf et al. 2014). The dimer β-receptor gp13 initiates signaling through activation of the JAK/STAT kinase signaling pathway. In this way, IL-6 and JAK/STAT pathways are linked to COVID-19 that generate cytokine storm (Ingraham et al. 2020).

Dysregulation of genes involved in infection-related approaches, including genes encoding cytokines and chemokines, has been shown to depend on atypical activation of NF-κB. (T. Liu et al. 2017). Over-activity of NF-κB was the motivation for the elevated production of cytokines and chemokines and thus development of COVID-19 (Gudowska-Sawczuk and Mroczko 2022) and consequently diabetes occurrence in the future.

NF-κB is a key transcriptional member of M1 macrophages (classical monocytes) and is a key inducer of various anti-inflammatory genes, such as TNF-α, IL-1β, IL-6, IL-12, p40, and cyclooxygenase-2 (Karami Fath et al. 2022; N. Wang et al. 2014). However, as a preliminary driving force for NF-κB activation, TNFα triggers the NF-κB signaling pathway and, through its receptor TNFR1 and intermediate sequence adapters, regulate expression of a number of numerous seasoned anti-inflammatory and anti-apoptotic genes (Aggarwal 2003; Berghe et al. 2014; Dutta et al. 2006). In terms of cytokine polymorphism, "A" allele of TNF-α is considerably expressed in patients with COVID-19 in evaluation to controls. Indicating that the TNF-α AA genotype is extra at risk of sickness and is linked to a more aggressive sample of the disease (Saleh et al. 2022). Consequently, TNF-α/NF-κB signaling may also play pathological roles in the immune cell stimulation in cytokine typhoon (CS) by inducing epithelial cells apoptosis, promoting epithelial–immune cell interaction and increasing systemic inflammation (L. Yang et al. 2021). Cytokine storm generated by activation of numerous anti-inflammatory signaling pathways has been cited as a main cause of death in COVID-19 patients (Ye et al. 2020). We also believe that SARS-CoV-2, probably like other RNA viruses, can induce oxidative stress (Cecchini and Cecchini 2020; Mehta et al. 2020) by interfering with key reactive oxygen and

nitrogen species such as superoxide anion radicals and nitric oxide. In addition to increased cytokine release and classic markers of acute inflammation, immune cells infiltration and progressive lymphopenia, especially the neutrophil to lymphocyte ratio is recognized as a prognostic marker (Y. Liu et al. 2020). This neutrophils infiltration in COVID-19results in the secretion of ROS and has been hypothesized to amplify both hyperinflammation and further damage to multiple body organs such as β cells (Tay et al. 2020). In addition to this, the imbalance between antioxidants and pro-oxidants leading to oxidative stress (OS) is also caused by a decline in antioxidant defenses in viral infections, leading to lipid peroxidation and DNA oxidation (Laforge et al. 2020).

COVID-19 and T1DM: the newly diagnosed type 1 diabetes mellitus (T1DM)

Since T2DM is the most common type of diabetes mellitus and because it is so frequent, evidence about the impact of diabetes mellitus on COVID-19 has not always distinguished between the primary forms. As mentioned in this section, some significant evidence is accessible specifically for T1DM (Tenforde et al. 2020). Patients with newly diagnosed T1DM were found to have ketoacidosis at the onset of COVID-19 in the reported case, while patients without ketoacidosis evolved symptoms some weeks later and emerged to have recovered from COVID-19 (Marchand et al. 2020; Potier et al. 2021). These findings suggest that SARS-CoV-2 is to blame for this metabolic disorder. One study included 29 patients, some of whom had an ordinary HbA1c level upon admission but developed hyperglycemia during COVID-19 treatment but had not previously been diagnosed with diabetes mellitus. The amount of pediatric T1DM patients admitted to Italian diabetes specialist centers was less than anticipated. In comparison, in specialized hospitals in northwest London, UK, a greater percentage number of individuals suffering from serious ketoacidosis was noted, indicating the potential for a rise in the frequency of newly diagnosed T1DM patients (Smith et al. 2021; Unsworth et al. 2020). Due to the small number of patients analyzed, these conflicting results may be due to chance or changes in access to healthcare during the COVID-19 pandemic. However, the same study found that among kids and teenagers with newly diagnosed T1DM, the incidence of diabetic ketoacidosis and severe ketoacidosis increased statistically significantly. A likely explanation for this finding is that patients tried to delay for hospitalization for fear of SARS-CoV-2. If there is a real link between COVID-19 and new-onset T1DM, it will become more evident as the COVID-19 pandemic develops and more patients are considered (Kamrath et al. 2020; Tittel et al. 2020) to investigate this correlation and propose some preventing/treating the patients. However, during the COVID-19 epidemic, there was considerable debate about the advantages and disadvantages of using ACE inhibitors or angiotensin receptor blockers. Alternative factors, such as ACE2, angiotensin-(1–7), angiotensin-(1–9), and the Mas receptor, may be necessary for the entry and SARS-CoV-2 infection progression in addition to the conventional RAAS (Novack et al. 2009). Due to the lack of evidence that RAAS inhibitors use in diabetes mellitus and COVID-19 causes harm, many international medical societies advise continued use (Papazian et al. 2013). Statins, or 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, are useful in treating bacterial and viral infections due to their anti-inflammatory and immunomodulatory properties. According to a Chinese study, hospitalized COVID-19 patients who took statins had a lower risk of all-cause mortality and a better recovery profile. RCTs are necessary to verify the statin's efficacy (Zhang et al. 2020).

Thromboembolic events in COVID-19 patients

Available data show that COVID-19 significantly increases the risk of thromboembolic, the leading cause of death (Fig. 2). Initial findings from China were the first to show aberrant coagulation parameters linked with COVID-19 (Klok et al. 2020). For instance, the baseline characteristics of the first 99 patients admitted to the hospital in Wuhan revealed that 36% had elevated D-dimer, 6% had elevated activated partial thromboplastin time, and 5% had elevated prothrombin time. Another study from China discovered statistically significant elevated levels of D-dimer and fibrin degradation products in patients who passed away from COVID-19 (Connors & Levy 2020). Only 0.6% of the survivors in this research of middle-aged Chinese patients with COVID-19 met the criteria for disseminated intravascular coagulation, while more than 71% of the dead did (Fei et al. 2020). Notably, 11 investigations have discovered increased incidences of venous thromboembolism in COVID-19 patients (N. Chen et al. 2020a), 2020b. The findings of laboratory tests can reveal minor differences in coagulation disorders linked to COVID-19 to disseminated intravascular coagulation with multiple organ failure and thrombosis. The coagulation problems are caused by a severe inflammatory response to SARS-CoV-2 infection. Vascular endothelial dysfunction may plays a role in the pathogenesis of microcirculatory alterations in patients infected with SARS-CoV-2 (Oxford et al. 2020). It is important to note that The ACE2 receptor on endothelial cells is an important pathway of infection for SARS-CoV-2. Replication of the virus leads to the infiltration of inflammatory cells, the death of endothelial cells, and the prothrombosis of microvasculature. Patients infected with SARS-CoV-2 and subsequently died showed signs of endothelial cell apoptosis, sequestered mononuclear and polymorphonuclear cell infiltration, and

viral inclusions in endothelial cells (Varga et al. 2020). Data show that dysregulation, endothelial cell death, and increased release of clotting factors are the main causes of increased thromboembolism in COVID-19 patients. Younger patients, patients with cardiac ischemia and thromboembolic complications, and cerebrovascular problems may all be associated with endothelial dysfunction (Iba et al. 2019).

Thromboembolic risk in patients with diabetes mellitus

In other studies, other than those related to the unique scenario of SARS-CoV-2 infection, it has been noted that patients with diabetes mellitus have an elevated risk of thromboembolism. For instance, a population-based study discovered that T2DM patients had a higher risk of venous thromboembolism than controls (HR 1.44, 95% CI 1.27–1.63). Additionally, patients with T2DM had higher pulmonary embolism risks compared to controls (HR 1.52, 95% CI 1.22–1.90) (Chung et al. 2015). Another study discovered that patients with diabetes mellitus had statistically considerably higher rates of deep vein thrombosis (DVT) than those without the condition following total knee replacement (Olesen et al. 2019). Additionally, it was discovered that diabetes mellitus increased the chance of developing an ulcer following a DVT by more than twice. Therefore, patients with diabetes mellitus are already at a high risk of having a stroke or thromboembolic event (Overvad et al. 2015). It is a disorder of platelet function in which the endothelium loses its ability to restrain prostacyclin (PGI2) and nitric oxide (NO) from acting on platelets. The hormone insulin naturally inhibits the hyperactivity of platelets. It enhances the generation of PGI2 and NO by the endothelial cells. So, a disordered platelet milieu is a consequence of the defects in insulin action in diabetes (Vinik et al. 2001). Patients with diabetes mellitus who are at risk of contracting SARS-CoV-2 infection should avoid remaining still for extended periods because frequent exercise is linked to a lower risk of thromboembolism. However, these patients should try to get active to enhance blood circulation. Ankle rotations and calf massages are two suitable, easy exercises that may be performed at home and must be suggested. Patients with potential thromboembolic problems should not delay contacting their physician if they develop chest pain, shortness of breath, or leg pain (Guo et al. 2019; Kunutsor et al. 2020).Because of the increased risk of thromboembolism in people with diabetes, the researchers suggest that physicians should give patients with diabetes mellitus an antiplatelet agent or anticoagulant to prevent thromboembolic during the COVID-19 pandemic. Current knowledge of the precise molecular and cellular mechanisms underlying the increased blood coagulability seen in COVID-19 patients is limited. Standard prophylaxis does not always appear to be successful in preventing thromboembolism. However, severe COVID-19 patients at high risk of thromboembolic, such as those with increased D-dimer levels, fared better when receiving anticoagulant medication (low molecular weight heparin). The translocation of NF-κB-p65 and the production of matrix metalloproteinases two and MCP-1, which are associated with a high risk of thromboembolism, were reduced by GLP1 administration in vitro. According to a cardiovascular outcome study, long-acting GLP1 analog dulaglutide therapy reduces the risk of stroke in T2DM patients. It would be advantageous for people with diabetes mellitus to select anti-diabetic medications that could lower the risk of thromboembolic events (Lim et al. 2021).

Association between COVID-19 treatment drugs and diabetes

In patients with diabetes mellitus, glucotoxicity, endothelial damage brought on by inflammation, oxidative stress, and cytokine production all raise the chance of thromboembolic consequences and harm to important organs (Fig. 2). Among COVID-19 patients without diabetes, a Chinese multicenter retrospective study found that high fasting blood glucose levels on admission (≥ 7.0 mmol/L (≥ 126 mg/dL)) were associated with higher mortality. It was suggested to be an independent predictor (S. Wang et al. 2020). Therefore, it is crucial to check blood sugar levels and treat worsening hyperglycemia in patients with advanced to severe COVID-19 phases. Despite this, during the COVID-19 pandemic, doctors unintentionally prescribed several drugs that directly or indirectly can cause hyperglycemia, insulin resistance and β cells dysfunction leading the more mortality of diabetic patients and also, increasing the high risk of diabetes in the future. Some of these drugs are mentioned bellow:

Corticosteroids

Antiviral medications or systemic corticosteroids, which are frequently used in the treatment of COVID-19 patients, may further aggravate hyperglycemia. In individuals with severe COVID-19, glucocorticoid medication presumably lowers cytokine production and prevents its harmful consequences. A study indicated that dexamethasone medication decreased mortality by 36% (HR 0.64, 95% CI 0.51–0.81) in patients undergoing invasive mechanical ventilation and by 18% (HR 0.82, 95% CI 0.72–0.94) in patients receiving just oxygen (Group 2020). This finding needs to be confirmed by other long-term investigations, especially in people with diabetes mellitus (Lim et al. 2021). Even in previously insulin-resistant or obese patients, chronic or high-dose corticosteroid use can cause the establishment of diabetes.

The increased risk of diabetes may be explained by modifications to the metabolism of carbohydrates, including insulin resistance and decreased peripheral glucose absorption. Although there is little research on the incidence and predisposing factors for corticosteroid-induced diabetes, it is anticipated that up to 20–54% of people who receive corticosteroids will develop the condition (De Micheli 2016; Suissa et al. 2010). The impact of glucocorticoids on people who have been diagnosed with diabetes is even more detrimental. According to studies, the use of glucocorticoids increases insulin resistance and hyperglycemia, which leads to uncontrolled diabetes in a dose-dependent way (Blackburn, Hux, and Mamdani 2002; Slatore et al. 2009). For more than 70 years, corticosteroids have been used to modify the immune response in a wide range of disorders. Through genomic and non-genomic effects, these medications have been demonstrated to prevent and reduce inflammation in tissues and blood circulation (Annane 2021). At low dosages, corticosteroids (dexamethasone and methylprednisolone) could lower mortality in people with severe COVID-19 disease, but they had no influence on the mortality rate in people with milder disease. Additionally, the excessive use of corticosteroids was not encouraged because the drug's high doses could harm rather than help (Ahmed and Hassan 2020). Diabetes brought on by glucocorticoids is a dangerous and underappreciated issue when the treatment plan is ineffective and poorly thought out (Elena et al. 2018). The worsening of glycemic control in diabetics as well as hyperglycemia or even the formation of new diabetes in those without previous diabetes are commonly observed side effects of glucocorticoids. As a result of their adverse effects on glycemic control, glucocorticoids increase insulin resistance (IR) (primarily in the liver and skeletal muscles) and cause β-cell dysfunction (Alabbood et al. 2019).

Carbohydrate metabolism is significantly altered during glucocorticoid administration, which results in insulin resistance, hyperglycemia, glycosuria, and subsequently increasing the hepatic gluconeogenesis. This effect appears to be related to the inhibitory effect of glucocorticoids on the conversion of pyruvic acid to acetyl-coenzyme A, resulting in pyruvic acid accumulation and glucose re-synthesis (Binder 1969; De Bodo and Altszuler 1958; Thorn et al. 1957). This impact is brought on by increased stimulation of gluconeogenic enzymes such as glucose-6-phosphatase, fructose-1,6-bisphosphatase, and phosphoenolpyruvate carboxykinase (Cassuto et al. 2005). Glucocorticoids also affect insulin secretion by decreasing the impact of incretins (a group of metabolic hormones that stimulate a decrease in blood glucose levels Fichna and Fichna 2017; Sato et al. 2015). Glucocorticoids have been demonstrated to have a pro-adipogenic effect. The genetic expression of pathways that maximize the effects of insulin appears to be a mediator of the lipogenic impact of these medications (Hillgartner et al. 1995). High levels of these medications in adipose tissue were linked to increased abdominal fat, decreased glucose tolerance, and hypertriglyceridemia when corticosteroid usage was assessed in animal models. Additionally, there was a decrease in serum levels of adiponectin and an increase in serum levels of TNF-α, which are connected to insulin sensitivity and resistance, respectively (Guia and Herzig, 2015). Additionally, glucocorticoids have a lipolytic effect that is particularly evident in peripheral fat. An increase in the activity of enzymes is mediated by the activation of transcription factors that control the function of lipases (Ebbert and Jensen 2013; Guia and Herzig 2015; Peckett et al. 2011). However, it is still unclear how corticosteroids would affect lipolysis over the short and long term.

Interferon-β (IFN-β)

In clinical trials, interferon-β (IFN-β) has demonstrated promising results for COVID-19 treatment (Salto-Alejandre et al. 2022). In phase 2 randomized trial, the immuno-modulator interferon beta-1b (IFN-β1b) in combination with protease inhibitors (lopinavir-ritonavir) and a nucleoside analogue (ribavirin) was preferable to lopinavir–ritonavir alone in reducing the time of viral shedding, symptom relief, and length of hospital stay in COVID-19 patients (Salto-Alejandre et al. 2022).

In addition to their antiviral properties, interferons also modulate immune responses. Interferon beta1-a (IFN-β1a) demonstrated considerable efficacy in COVID-19 patients in a recent clinical trial. Previous in vitro studies demonstrated interferon-β antiviral efficacy against the SARS virus (Fallahzadeh et al. 2022). Both types of IFNs may cause diabetes mellitus because it has been documented that long-term therapeutic use of type I IFNs causes autoimmunity as well as the emergence of type 1 diabetes after treatment with type I IFNs (Pelegrin et al. 1998). In a study, a 57-year-old man had 7 weeks of interferon therapy. His blood glucose level gradually rose while interferon therapy was continued in the outpatient clinic, and he was admitted to the hospital for hyperglycemia (Kado et al. 2000). In addition, a 57 year-old woman who had IFNβ-1a therapy for multiple sclerosis was identified as having diabetic ketosis (Uonaga et al. 2012). A selective failure to secrete insulin in response to glucose, together with greater responsiveness to other secretagogues, is characteristics of type 1 diabetes in its early stages. The autoimmune reaction against the β-cells may be the cause of the inadequate glucose response. When pancreatic islets are cultured in the presence of certain cytokines, their function is altered. These

cytokines may be the cause of immunologic damage to β-cells. M Pelegrin et al. demonstrated that pancreatic beta-cell function may be affected by IFN-β both in vitro and in vivo. The results show that IFN-β may change the signals that result in an increase in insulin production in response to glucose in islets grown in the presence of IFN-β or in islets from transgenic mice expressing the RIP/IFN-β chimeric gene (Pelegrin et al. 1998). All of the studies presented here suggest that IFN-β may have a direct role in diabetes development.

Selenium

In cells infected with SARS-CoV-2, the activity of cytotoxic effector cells is improved by selenium. The maintenance of T cell maturation and functions, as well as the synthesis of T cell-dependent antibodies, depend on selenium (Bae and Kim 2020). Serum levels of selenium were measured in 50 COVID-19 patients. 42% of them were deficient in selenium (Im et al. 2020). Given the complexity of the effects of different selenium species on glucose metabolism in humans and animals, the association between selenium overexposure and diabetes risk has biological plausibility. According to the generally intriguing ability of selenoproteins to exert both favorable and unfavorable effects on biological systems, a wide variety of potential interests in diabetes development have emerged through selenium species themselves and selenoprotein overexpression. It can actually have harmful adverse effects (Vinceti et al. 2018). For instance, it assumes a basic part in the union of selenoprotein P, a physiological selenium carrier, and in the combination of hepatic gluconeogenesis. As proliferator-activated receptor gamma coactivator 1α (PGC1α) is upregulated in the livers of diabetic creatures and advances insulin opposition, we speculate that dysregulated pathways in carbohydrate metabolism and aggravation of selenium homeostasis are connected through PGC1α (Steinbrenner et al. 2010).

Glucose-lowering drugs

The therapy of patients with diabetes mellitus and COVID-19 may be affected by the potential impact of routinely used glucose-lowering drugs on COVID-19 development.

Dipeptidyl peptidase 4

Dipeptidyl peptidase 4 (DPP4, known as CD26, generally plays an important role in glucose homeostasis. (Drucker 2006). DPP4 is also important in immunity (referred to as I-TAC) as a marker of activated T cells and a regulator of many chemokines, including CCL5, CXCL12, CXCL2 (also known as GRO-b), and CXCL11 (Lambeir et al. 2003; Metzemaekers et al. 2016). DDP4 inhibitors (DPP4is) are frequently used to treat type 2 diabetes by decreasing blood glucose. According to reports of upper respiratory tract infections, there have been problems with the elevated risk of viral infection with DPP4 inhibition. However, clinical trial data on DPP4 use and the risk of community-acquired pneumonia in people with type 2 diabetes do not support an elevated risk (Gorricho et al. 2017; Willemen et al. 2011). Even though ACE2 is the primary receptor, DPP4 has the potential to bind to SARS-CoV-2. Strangely, several DPP4 protein variants found in Africans were linked to a lower risk of MERS-CoV infection. DPP4 plasma levels, on the other hand, were statistically substantially lower in MERS-CoV patients, indicating a protective role for DPP4. It's unclear whether DPP4's ability to function as a viral receptor is affected by DPP4 (Inn et al. 2018; Kleine-Weber et al. 2020; Mahase 2020). DPP4 expression appears to be altered in the spleen, liver, kidney, lung, and some immune cells of T2DM patients (Mulvihill & Drucker 2014). DPP4 is also released into the bloodstream as soluble DPP4, not simply as a cell membrane protein. There is indecision about the potential role of soluble DPP4 as a viral receptor or as a protective factor during SARS-CoV-2 disease (Varin et al. 2019). In-vitro research with the DPP4 inhibitors sitagliptin, vildagliptin, or saxagliptin did not prevent coronavirus entry into cells (Raj et al. 2013). Interactions between DPP4 and the RAAS (including ACE2) appear likely, despite a lack of research (230, 231). The genetic link between DPP4 and RAAS is associated with an increased risk of COVID-19 infection and SARS-CoV-2 exposure, especially in patients with diabetes mellitus (Valencia et al. 2020). DPP4 expression was found to be increased in blood T cells from T2DM patients. It was linked to insulin resistance, and overexpression of DPP4 in diabetic mice was associated with dysregulation of immune responses, all of which lend support to this link (S. A. Lee et al. 2013; Romacho et al. 2020). In patients with T2DM, DPP4 treatment was found to be neutral, not superior, in terms of serious side effects, including cardiac events, including stroke (Lim et al. 2020; Nauck et al. 2017). DPP4 suppression has been shown to support the cardiovascular system through anti-inflammatory properties such as the reduction of oxidative stress and endoplasmic reticulum stress. On human $CD4^+$ and $CD8^+$ T lymphocytes, the receptor-binding domain of DPP4 interacts with adenosine deaminase (ADA). This discovery implies that SARS-CoV-2 may alter the host's immune system by binding to DPP4 and competing for the ADA recognition site. As a result, treating SARS-CoV-2 infection may require the use of the DPP4 receptor binding domain (Raj et al. 2014). Particularly, following systemic DPP4 suppression with DPP4is, circulating levels of inflammatory markers were raised in a mouse model fed conventional chow. On the other hand, treatment with DPP4i did not increase inflammatory markers in humans, despite

decreasing the activity of the DPP4 enzyme. Based on these results, it appears there may be a difference between DPP4 enzyme activity and DPP4i use in humans and animals (Baggio et al. 2020). There are no known safety concerns with DPP4is in T2DM and COVID-19 patients (Iacobellis 2020). The use of sitagliptin while a patient was hospitalized was linked to lower mortality and better clinical outcomes in a retrospective case–control study from northern Italy. Although this finding was based on just 11 individuals, a different Italian case series demonstrated the correlation between DPP4i medication and a statistically significant decreased mortality (of whom one died) (Mirani et al 2020; Solerte et al. 2020). However, compared to 49 individuals with T2DM treated with conventional glucose-lowering drugs, 27 patients treated with DPP4i had worse outcomes (mortality findings were not reported) (Dalan et al. 2021). Therefore, to evaluate the possible survival improvements associated with DPP4 inhibition in individuals with COVID-19 patients, which might extend to patients without diabetes mellitus, prospective randomized clinical studies (RCTs) in relevant population's o are required.

Glucagon-like peptide 1 and its analogues

In cardiovascular outcome tests, treatment with the majority of glucagon-like peptide 1 (GLP1) analogs decreased the number of significant adverse cardiac events in patients with T2DM (Lim et al. 2020). There are several pleiotropic effects associated with GLP1 (for example, on immunity and inflammation) when the GLP1 receptor is activated. GLP1 receptors are found in many human tissues and organs, such as kidneys, lungs, endothelial cells, hearts, and nerve cells (Drucker 2006; Lim et al. 2018; H. Liu et al. 2009). GLP1-based treatments reduce the production of numerous inflammatory cytokines and immune cell invasion in these organs. Exendin 4, a GLP1 analog, greatly reduced monocyte and macrophage levels in the arterial wall in atherosclerosis animal models and inhibited atherogenesis by controlling inflammation in macrophages (Arakawa et al. 2010). Furthermore, exendin 4 demonstrated renoprotective properties in animal models by decreasing NF-κB activity in the kidney, and enhanced NF-κB activity plays a role in oxidative stress and inflammation (Kodera et al. 2011). With lipopolysaccharide or TNFα stimulation of human aortic endothelial cells in vitro, liraglutide therapy, a GLP-1 receptor agonist, decreased the expression of vascular cell adhesion molecule 1 (Y.-S. Lee and Jun 2016). Liraglutide was also given to C57BL/6 mice that were fed a high-fat diet to decrease inflammation and lipid accumulation in the heart. Infusions of native GLP1 in T1DM patients decreased IL-6, intercellular adhesion molecule 1, and oxidative stress markers in the blood (Noyan-Ashraf et al. 2013). GLP1 and GLP1 analogues have been shown to effectively treat chronic inflammatory diseases in humans, including non-alcoholic fatty liver disease, atherosclerosis, and neurodegenerative diseases. These effects appear to be mediated primarily by reduced activity of inflammatory pathways. It is yet unknown if these benefits of low-grade inflammation linked to atherosclerosis convert into anti-inflammatory effects important to the COVID-19 disease process. Based on such qualities, however, there is little reason to worry about the prolonged use of GLP1 analogs in patients with diabetes mellitus and COVID-19, since during COVID-19, persons with cardiovascular or kidney diseases had worse outcomes than those who did not have these conditions. Therefore, it would appear reasonable to protect the cardiorenal system's integrity in those at high risk of SARS-CoV-2 infection.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors

To treat T2DM, sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT2is) work on the kidney to decrease blood glucose levels. In T2DM patients treated with SGLT2, inflammatory cell infiltration into arterial plaques was reduced, as were cytokines and chemokines including TNF, IL-6, and monocyte chemoattractant protein 1 (MCP1) (Garvey et al. 2018; Han et al. 2017). Ketoacidosis can occur with SGLT2i therapy, particularly in critically ill patients. In addition, both urate crystal-dependent and crystal-independent mechanisms have been implicated as risk factors for acute kidney injury due to high urinary uric acid excretion. SGLT2is has a significant impact on urinary glucose and sodium excretion, resulting in osmotic diuresis and potential dehydration (Hahn et al. 2016, 2017). As an outcome, using SGLT2 in patients who require critical care and precise control of their fluid balance could be difficult. Moreover, in the presence of a reduced estimated glomerular filtration rate, which reduces their ability to control blood sugar and is a challenge in patients with critical illnesses, these therapies must be discontinued. However, a worldwide study is currently being conducted to compare the effectiveness of dapagliflozin, administered once daily for 30 days, to a placebo in reducing disease progression, complications, and all-cause death in COVID-19 patients admitted (NCT04350593). The findings of this study may provide light on the potential effects of SGLT2is therapy on these kinds of patients (Lim et al. 2021).

Thiazolidinedione

The thiazolidinediones are agonists of the peroxisome proliferator-activated receptor-γ (PPARγ), a nuclear receptor that controls the transcription of several genes involved in lipid and glucose metabolism (Yki-Järvinen 2004). In numerous primary and experimental studies, thiazolidinediones have been shown to reduce insulin resistance and to have

Table 1 Drugs associated with diabetes during COVID-19 treatment

Drug	Target	Description/mechanism	References
Corticosteroids	β-Cell	1) Inhibiting the conversion of pyruvic acid to acetyl-coenzyme A	Binder 1969; De Bodo & Altszuler 1958; Thorn et al. 1957
		2) Decreasing the impact of incretins	Fichna & Fichna 2017; Sato et al. 2015
Interferon-β	β-Cell	Autoimmune reaction against the β-cells	Pelegrin et al. 1998
Selenium	PGC1α	Insulin resistance	Vinceti et al. 2018
DPP4	T lymphocytes	Insulin resistance	Raj et al. 2014
			S. A. Lee et al. 2013; Romacho et al. 2020
GLP1 Exendin 4	Kidneys, lungs, heart, Endothelial cells, and Nerve cells	Reducing NF-κB activity	Drucker 2006; Lim et al. 2018; H. Liu et al. 2009
SGLT2is	Kidney	Affects urinary glucose and sodium excretion	Hahn et al. 2016; Hahn et al. 2017
Thiazolidinedione	Agonists of the PPARγ	Controls the transcription of several genes involved in lipid and glucose metabolism	Yki-Järvinen 2004

potential anti-inflammatory and antioxidant activities, which may contribute to their antiatherosclerotic properties (A. C. Li et al. 2000). Thiazolidinediones may have cardiovascular protective effects due to their properties. In a review, thiazolidinedione treatment was found to be more effective than a placebo in the secondary prevention of stroke and related vascular events in patients who had previously experienced a stroke or transient ischemic attack. However, thiazolidinedione medication has been linked to weight gain, edema, and, more importantly, the worsening of heart failure. These findings call into question the use of thiazolidinedione in Coronavirus patients. More clinical preliminary studies are predicted to update the risk–benefit ratio of using thiazolidinediones in patients with COVID-19 (Kernan et al. 2016; Jia Liu & Wang 2015). Drugs associated with diabetes during COVID-19 treatment are listed in Table 1.

Proposed treatment strategies of SARS-CoV-2-infected diabetic patients

The global COVID-19 pandemic has improved the investigation into effective SARS-CoV-2 infection prevention and therapy. There are now more than 1,800 clinical trials focused on the viral entrance, replication, and immunological responses to infection; nevertheless, most medications' efficacy has not yet been established. Candidates for COVID-19 therapy can influence glucose metabolism by manipulating inflammation and the immune system or pharmaceutically. Therefore, patients with diabetes mellitus should take special care when using these medications (Lim et al. 2021).

Antiviral therapies

A serine protease inhibitor called camostat mesylate has been investigated for its potential to prevent viral entry because it inhibits the transmembrane protease serine 2 (TMPRSS2), which facilitate viral entry into the host cell. Camostat mesylate therapy reported to reduce the risk of new-onset diabetes in patients with chronic pancreatitis. In animal models, this medication reduced fat accumulation and improved insulin resistance and glycemia. Given their possible side effects, the antimalarial drugs chloroquine and hydroxychloroquine are to treat SARS-CoV-2 infection. It is believed that hydroxychloroquine's anti-inflammatory and immunomodulatory properties and restriction of viral spike protein cleavage at the ACE2 binding site are its two major mechanisms of action. Hydroxychloroquine is approved for use as an anti-diabetic drug in several countries due to its ability to lower glucose levels while improving pancreatic beta-cell function and insulin sensitivity. In the rare case that a diabetic uses hydroxychloroquine, it may be necessary to change existing antidiabetic medications to prevent hypoglycemia. It's important to note that studies on the efficacy of hydroxychloroquine in treating COVID-19 patients have shown conflicting results. It is believed that more carefully designed studies are needed to determine its therapeutic effects. Inhibitors of the protease enzyme, like lopinavir and ritonavir, can be toxic to patients with pre-existing diabetes, contribute to hyperglycemia and new-onset diabetes, and rarely cause diabetic ketoacidosis (high blood sugar). These drugs reduced insulin sensitivity and β-cell function in HIV patients by up to 50%. The pharmacological effects of co-administration of hypoglycemic drugs are another issue with protease inhibitors. For example, ritonavir acts as a CYP3A4/5 inhibitor, increases plasma levels of the

DPP4 inhibitor saxagliptin, and acts as an inducer of the enzyme uridine-5'-diphospho-glucuronosyltransferase, thereby inhibiting SGLT2 and reduces levels of the drug canagliflozin. It is recommended that patients taking these drugs monitor their blood glucose levels frequently and adjust their doses as necessary. Remdesivir, an RNA-dependent RNA polymerase nucleotide analog inhibitor, ameliorated hyperglycemia, insulin resistance, fatty liver, and endotoxemia in mice fed a high-fat diet. Despite this, remdesivir-treated and placebo-treated patients increased their blood glucose levels similarly in two RCTs with multiethnic groups, including Chinese patients. Therefore, more data are required to clarify its impact on glucose metabolism (Dequin et al. 2020).

Adjunctive therapies

Combination medications are used during the hyperinflammatory phase of COVID-19 to prevent the disease from progressing to more serious forms such as ARDS and multiple organ failure. These medications can also affect how glucose is metabolized. For instance, IL-6 receptor inhibitors, a potential therapeutic option for COVID-19 patients with severe disease, significant pulmonary lesions, and high IL-6 levels, are associated with impaired glucose tolerance and insulin resistance in patients with rheumatoid arthritis. Anakinra, an IL-1β inhibitor that significantly improved respiratory function in patients with severe COVID-19, enhanced glycemia and β-cell function in T2DM patients (Dimopoulos et al. 2020). Canakinumab, another IL-1β inhibitor being tested in a clinical trial for the treatment of COVID-19, was unsuccessful in treating T1DM that had recently developed. Other prospective COVID-19 therapeutic options, such as JAK 1/2 inhibitors and Bruton's tyrosine kinase inhibitors, reduced glycemia and insulitis while impairing levels of anti-insulin B lymphocytes and insulin antibodies, which may play protective roles in T1DM. Adalimumab is one of the TNF inhibitors that hold promise for treating COVID-19's inflammatory stage. In individuals with active rheumatoid arthritis, TNF inhibitors reduced hyperglycemia, insulin resistance, and β-cell function. It is generally recognized that systemic corticosteroids cause hyperglycemia, mainly through raising postprandial glucose levels, insulin resistance, and β cell dysfunction, which frequently requires the start of insulin therapy. According to this concern, patients with severe ARDS and COVID-19 experienced a statistically significant increase in ventilator-free days after receiving intravenous dexamethasone therapy. Further, a meta-analysis of clinical studies found that patients with severe COVID-19 benefit from systemic corticosteroid therapy (Sterne et al. 2020). Different hydrocortisone regimens also demonstrated a propensity to improve these individuals' hospital courses. Another investigation, however, was unable to demonstrate any positive effects of low-dose hydrocortisone in the care of COVID-19 patients. These unsatisfactory findings could be attributed to a suboptimal dose. The impact of pharmacological COVID-19 therapies on people with diabetes mellitus' glucose metabolism needs to be studied more thoroughly (Dequin et al. 2020).

Anticoagulant drugs

Investigational drugs for COVID-19 may interfere with routinely used oral anticoagulants or antiplatelets (Lim et al. 2021). In some countries, such as China and India, patients with COVID-19 are empirically treated with a combination drug containing the protease inhibitors lopinavir and ritonavir. These protease inhibitors reduces the levels of the active metabolite of the antiplatelet drug clopidogrel by inhibiting the metabolism of the cytochrome P450 3A4 (CYP3A4) enzyme (Driggin et al. 2020). In contrast, by inhibiting ticagrelor metabolism, these protease inhibitors may enhance its anticoagulant effect. Taking vitamin K antagonists, such as apixaban and betrixaban, with protease inhibitors can adversely affect dose adjustment requirements. Conversely, lopinavir and ritonavir should not be used with the oral anticoagulants edoxaban and rivaroxaban that do not contain vitamin K antagonists. This is because the anticoagulant effects of these drugs are significantly enhanced. (Mueck et al. 2013). Because CYP3A4 is involved in the metabolism of antiplatelet medicines and anticoagulant drugs, caution should be exercised when prescribing medications that may affect CYP3A4 activity. Remdesivir, a nucleotide analogue inhibitor of RNA-dependent RNA polymerase, has shown positive results in reducing the length of hospitalization for COVID-19 patients. Anticoagulants or antiplatelets have not been shown to interact significantly with Remdesivir. Parenteral anticoagulants and experimental COVID-19 therapeutics are not known to interact significantly. When considered as a whole, it makes sense to evaluate the risk of thromboembolism in patients with diabetes mellitus and take pharmacological thromboprophylaxis into account, especially if such individuals also have other thromboembolic risk factors or are hospitalized with COVID-19 (Sanders et al. 2020). The proposed drugs that may be beneficial for diabetes prevention/SARS-CoV-2 infected diabetic patients are listed in Table 2.

Inactivity

In addition to the complications of COVID-19 and the drugs used during the pandemic, quarantine and inactivity may also be among the factors that can lead to diabetes.

Table 2 Proposed drugs that may be beneficial for diabetes prevention/SARS-CoV-2-infected diabetic patients

Drug	Target	Description/Mechanism	References
Camostat mesylate	TMPRSS2	1) The virus is prevented from entering the host cell by inhibiting the transmembrane protease serine 2 (TMPRSS2) 2) Reducing fat accumulation and improving insulin resistance and glycemia	Dequin et al. 2020
Hydroxychloroquine	β-Cell	Ability to lower glucose levels while also enhancing pancreatic beta-cell function and insulin sensitivity	Dequin et al. 2020
Ritonavir	β-Cell	CYP3A4/5 inhibitor, enhancing plasma concentration of the DPP4 inhibitor saxagliptin, and as an inducer of the enzyme uridine 5′-diphospho-glucuronosyltransferase, reducing amounts of the SGLT2 inhibitor canagliflozin	Dequin et al. 2020
Anakinra	β-Cell	IL-1β inhibitor	Dimopoulos et al. 2020
JAK 1/2 inhibitors & Bruton's tyrosine kinase inhibitors	Anti-insulin B Lymphocytes	Impairing levels of anti-insulin B lymphocytes and insulin antibodies	Sterne et al. 2020

Governments tightened the quarantine and ordered everyone to stay at home as much as possible in an effort to stop the spread of COVID-19. These actions have negative effects on people's quality of life. As well as other things, there is considerable concern about the harmful consequences of inactivity. All athletic competitions have been postponed or canceled (Crisafulli and Pagliaro 2021). The pandemic itself (and the various restrictions to limit the spread of the virus) will help ensure that evidence-based interventions (such as behavior change training) and national policies (such as providing safe facilities for walking and cycling), COVID-19 features were not properly used to encourage physical activity before or during the pandemic. Regardless of age, medical condition, or location, most studies reported a significant decline in both self-reported or objectively assessed physical activity, as well as an increased inactivity (sitting), when comparing pre-COVID-19 periods with the COVID-19 lockdowns and/or post-COVID-19 periods (Varela, Sallis, Rowlands, and Sallis 2021). Additionally, COVID-19 significantly reduces respiration and blood oxygen levels and decreases movement and physical activity. Low-intensity rehabilitation and breathing activities combined with medication can help patients with their blood oxygen levels, blood pressure, hand power status, and resting heart rate, which may help the recovery process go more quickly (Hekmatikar et al. 2021). In reality, different target parameters (such as glucose management, blood pressure, cholesterol status, or body composition) can be improved by exercise training in patients (Kemps et al. 2019). 90% of instances of diabetes are type 2 cases, which are usually brought on by obesity and a sedentary lifestyle (Lewis et al. 2019). Studies have shown that insulin resistance develops in human skeletal muscle when circulating plasma fatty acid content is increased (Venables and Jeukendrup 2009). According to Belfort et al., an increase in circulating fatty acids within the physiological range is associated with a reduction in insulin receptor substrate (IRS)-1 tyrosine phosphorylation, insulin-stimulated insulin receptor tyrosine phosphorylation, IRS-1 associated phosphatidylinositol (PI) 3-kinase activity, Akt serine phosphorylation, and glucose disposal rates (Belfort et al. 2005). Lipid infusion is related to an increase in long-chain acyl-CoA and diacylglycerol content within skeletal muscle, as well as decreased insulin activation of IRS-1 tyrosine phosphorylation and IRS-1-associated PI3K activity (Venables and Jeukendrup 2009).

Conclusions and future directions

Due to its high contagiousness and link to rising mortality rates, COVID-19 is evolving into a concern to world health. Patients with COVID-19 who were in the late stages of the disease experienced extraordinary lymphocytopenia and an inflammatory cytokine storm that damaged multiple organs such as β cells of the pancreas. The pathogenesis of SARS-CoV-2 infection demonstrates immunological dysregulation with NF-κB, a well-known inflammatory pathway, playing a significant role. As a result of the NF-κB's cycle, which results in inappropriate $CD4^+$ T cell differentiation and increased inflammatory signals, various organs become implicated in producing pro-inflammatory cytokines, which in turn generates a cytokine storm. Conversely, diabetes mellitus is a metabolic condition strongly linked to obesity and insulin resistance. It has been discovered that the inflammatory process plays a crucial role in the development/progression of diabetes or even competent the SARS-CoV-2 infected individuals to it. It is taking into consideration that people with diabetes are more prone to becoming infected with COVID-19 and mortality. Because SARS-CoV-2 exacerbates inflammation and modifies immune system responses, coronavirus infections have been shown to affect the management of diabetes

mellitus significantly. In addition to raising the risk of thromboembolism, SARS-CoV-2 infection is more likely to cause cardiorespiratory failure in people with diabetes mellitus than those without the condition. It is thought that each of these pathways has a role in the dismal prognosis of COVID-19 and diabetes mellitus patients (Fig. 2). For people with diabetes during the COVID-19 pandemic, strict glycemic control and managing cardiovascular risk factors are essential. So, patients with diabetes mellitus should follow the clinical recommendations for managing diabetes mellitus more carefully during the COVID-19 pandemic because COVID-19 can increase blood glucose levels. Moreover, as controlling inflammation is a crucial part of treating COVID-19 and diabetes mellitus, during the COVID-19 pandemic, some drugs were used that unwantedly lead to an increase in the inflammation/ROS competing the SARS-CoV-2-infected individuals to diabetes. In this line, for patients and healthcare professionals, we provide the following essential advice: patients should be more careful about adhering to prescribed prescriptions (including insulin injections) and their blood glucose levels, which should be tested more regularly than previously. Patients should see a doctor if their blood glucose levels are consistently higher than average. Healthcare professionals need more emphasis on healthy food intake and physical activity in patients with diabetes mellitus in light of current worldwide quarantine policies. Patients should be recommended to see their physician immediately if symptoms include a dry cough, increased sputum production, fever, or a fast rise in blood sugar. Additionally, patients are strongly advised to carefully follow their physician's recommendations and avoid statements spread through other media, including the internet, as they frequently do not hold up to scientific scrutiny.

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Declarations

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