Reviews in Cardiovascular Medicine

Systematic Review

# SARS-CoV-2 infection in patients with diabetes mellitus and hypertension: a systematic review

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After the emergence of the novel 2019 coronavirus disease in P. R. China, this highly contagious disease has been currently spread out to almost all countries, worldwide. Novel 2019 coronavirus disease, Middle East respiratory syndrome, and severe acute respiratory syndrome are reported to cause a higher risk for severe infections in patients with chronic comorbidities, such as hypertension and diabetes. These severe infections can contribute to higher rates of morbidity and mortality in these patients. In the present review, we discussed the role and underlying mechanisms of the two most common chronic diseases, type-2 diabetes mellitus and hypertension, in clinical manifestations and disease severity of novel 2019 coronavirus disease, Middle East respiratory syndrome and severe acute respiratory syndrome, with the hope to provide evidence for better decision-making in the treatment of this vulnerable population.

## Keywords

Diabetes mellitus; hypertension; SARS-CoV-2; COVID-19; MERS; SARS

## 1. Background

In mid-December 2019, the novel coronavirus disease 2019 (COVID-19) emerged in Wuhan, P. R. China. Up to now, COVID-19 has spread out to almost all countries worldwide and by July $31^{th}$, 2020, almost 17, 499, 767 individuals have been affected by this virus (World Health Organization., 2020). According to previous reports on two formerly coronavirus outbreaks, namely the severe acute respiratory syndrome (SARS) in Beijing, P. R. China in 2002 (with more than 8000 confirmed cases) (Chan-Yeung and Xu, 2003; Huang et al., 2009) and the Middle East respiratory syndrome (MERS) in Saudi Arabia in 2012 (with more than 2000 confirmed cases), and based on available data on COVID-19, the most prevalent comorbidities of intensive care units in the patients with these infectious diseases were identified as diabetes mellitus (DM), hypertension, cerebrovascular diseases, and coronary heart diseases (Fang et al., 2020; Guan et al., 2020; Madjid et al., 2020; Yang et al., 2020).

SARS-CoV and SARS-CoV2 bind to angiotensin-converting enzyme 2 (ACE2) on the surface of their target cells. In this regard, ACE2 is expressed by epithelial cells in the lungs, kidneys, and intestine (Wan et al., 2020). In patients with either type-1 or type-2 diabetes mellitus, as a response to the treatment by ACE inhibitors and angiotensin II type I receptor blockers (ARBs), the expression of ACE2 is remarkably increased (Fang et al., 2020; Wan et al., 2020). Hypertension can also be treated by the upregulation of ACE2 via ARBs and ACE inhibitors (Li et al., 2017b). Under these chronic conditions, it can also be suggested that ACE2 expression increases in response to the treatment with ACE inhibitors and ARBs. Such an increase in the expression of ACE2 can make the patient vulnerable to COVID-19 infection, as a result (Fang et al., 2020). At the time of SARS outbreak, there was also some evidence suggesting that diabetes from one hand can be a risk factor for SARS infection, contributing to poor prognosis in the patients, and from the other hand, SARS-CoV can also damage Langerhans islets, contributing to acute insulin-dependent diabetes mellitus in these patients (Yang et al., 2010). Therefore, this review aimed to elucidate the role and underlying mechanisms of chronic conditions, including DM and hypertension, in clinical manifestations and disease severity of COVID-19, MERS and SARS.

## 2. Method

We searched the electronic databases of Pubmed, Google Scholar, Excerpta Media Database (EMBASE), Web of Science and ResearchGate, in an attempt to find all articles relevant to the associations of hypertension and/or diabetes with COVID-19,

SARS or MERS, published from January $1^{st}$ 2003 until March $30^{th}$ 2020. We applied no limitation to the language of articles. The search strategies used for each database were separately designed and MeSH terms were included. Our search strategy was as follows:

    #1 'COVID-19'
    #2 'SARS-CoV-2'
    #3 'SARS'
    #4 'SARS-CoV'
    #5 'MERS'
    #6 'MERS-CoV'
    #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
    #8 'Hypertension'
    #9 'Diabetes'
    #10 #8 OR #9
    #11 #7 AND #10

We included all observational studies conducted on diabetic and/or hypertensive adult patients with confirmed COVID-19, SARS, and MERS. We, then, excluded those articles concerning coronaviruses other than the SARS-CoV2, SARS-CoV and MERS-CoV. Similar and duplicate studies were also excluded. Screening the title and abstract of the articles, we selected the relevant studies. After obtaining the full text of selected articles, we also reviewed the reference sections to identify any additional study.

## 3. Results

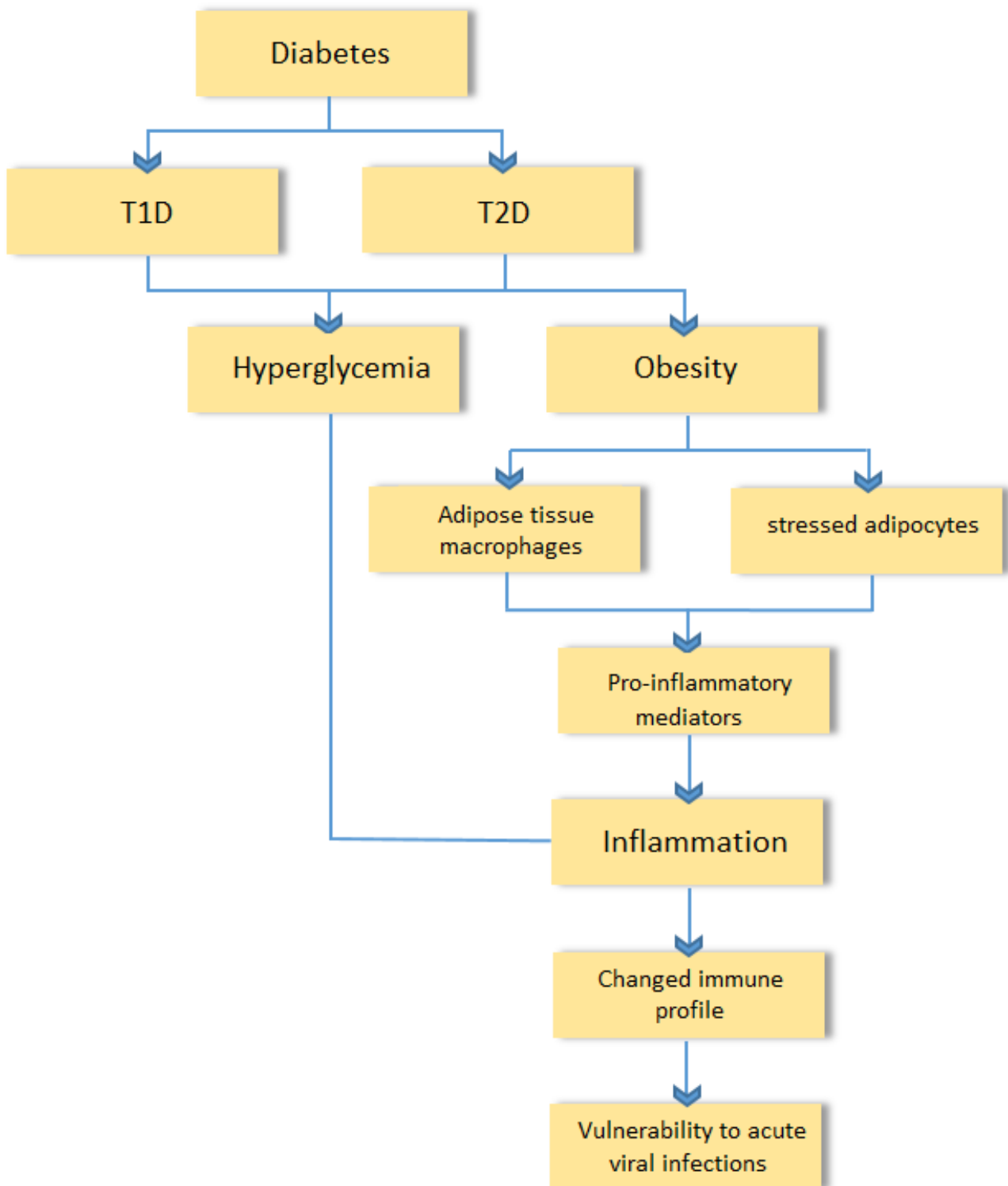### 3.1 The role of diabetes mellitus and hypertension in acute respiratory infections

Coronaviruses can cause intestinal and/or respiratory infections in animals and humans (Cheng et al., 2007). Severe respiratory infections, such as respiratory syncytial virus, influenza and bacterial pneumonia, are known as cardiovascular disease (CVD) triggers (Cowan et al., 2018; Madjid et al., 2007). Also, the existence of underlying CVD is normally associated to comorbidities, which can probably cause an increase in the infectious diseases severity and incidence (Dhainaut et al., 2005). Hypertension is recognized as one of the strongest risk factors for nearly all various CVDs, during life (Kjeldsen, 2018).

Worldwide, more than 425 million people are living with diabetes, which can be classified as type 1 (T1D) and type 2 diabetes (T2D) groups (Kulcsar et al., 2019). Diabetes complications are frequent among patients with both types of diabetes and are also responsible for considerable rates of morbidity and mortality. Accordingly, poorly controlled diabetes may lead to several complications including neuropathy, retinopathy, nephropathy, foot ulcers, dental diseases and increased risks of infections, as well (Moosaie et al., 2020; Papatheodorou et al., 2018). Notably, both types of diabetes lead to hyperglycemia, but with different mechanisms. T1D is usually resulted from an autoimmune-like condition that causes damage in pancreas $\beta$ cells, and consequently, reduction in producing insulin. However, T2D is developed when the body cannot properly respond to insulin. The most common type of diabetes is T2D, which consists about 85% to 95% of diabetic cases throughout the world (Ebrahimpour-Malekshah et al., 2020; Kulcsar et al., 2019). Etiologically, T2D is highly linked to obesity as well as the outcomes of chronic inflammation caused by excess adipose tissue. Many pro-inflammatory mediators are secreted by adipose tissue macrophages and stressed adipocytes, which can cause chronic low-degree inflammation. Such an inflammation may reduce the responsiveness of cells to insulin, and thus, change the regulation of homeostatic glucose (McLaughlin et al., 2017; Zmora et al., 2017). The main physiological T2D characteristics may be caused by hyperglycemia, glucose intolerance, and hyperinsulinemia. Mice and humans with T2D have shown changes from anti-inflammatory macrophages and predominately regulatory and T regulatory cells (T-regs) within the adipose tissue into T helper 1 (Th1) and T helper 17 (Th17) CD4 positive T cells and the predominately pro-inflammatory macrophages, as well (Meshkani and Vakili, 2016; Xia et al., 2017). It is believed that such changes in the immune system profile can result in different T2D-related implications, like more vulnerability against infection (Hodgson et al., 2015). Also, diabetes might weaken the innate immune system (Badawi et al., 2010) and make individuals more sensitive to a range of infectious diseases and severe illnesses (Badawi et al., 2010; Dooley and Chaisson, 2009). For example, when seasonal influenza epidemics happen, the patients with diabetes, compared to healthy cases, are reported to have 6- fold greater risk for becoming severely ill, 4-fold higher risk for pneumonia-related hospitalizations and a 3-fold increased chance for death due to its complications (Badawi et al., 2015). In addition, diabetes has several features and complications in common with infectious diseases such as the pro-inflammatory state, endothelial dysfunction and the innate immune response weakening (Badawi et al., 2010). In an acute viral infection, the shift of Th1, with microbicidal function by IFN$\gamma$ to Th2, with an anti-inflammatory function by IL-4, IL-5, IL-10, and IL-13, is related to a cytokine overload, which together with diabetes, can induce a rise in cytokines level, harm the endothelium, and consequently result in some complications (Dharmashankar and Widlansky, 2010). The Th1-to-Th2 shift and dampened innate immunity responses are reported to be involved in linking the observed high prevalence rates of allergy in lethal viral infections, such as Dengue fever (Toledo et al., 2016). Diabetes can also damage the functions of lymphocytes and macrophages, which may subsequently result in diminished levels of immune response (Dooley and Chaisson, 2009). Diabetes-related cellular insulinopenia and hyperglycemia are also known to damage the functions of macrophages and lymphocytes, and as a result, to cause a reduced level of immune response (Dooley and Chaisson, 2009). Moreover, HbA1c values $\geq$ 9% are reported to be connected with a 60% higher risk of pneumonia-associated complications and hospitalization, due to decreased levels of immune response (Kesavadev et al., 2012). Besides, the individual defense against infection, which is highly mediated by cellular immunity and the synthesis of associated cytokines, such as interleukins and IFNs, is down regulated in diabetes (Arora et al., 2011; Badawi et al., 2010) (Fig. 1).

### 3.2 Diabetes mellitus and hypertension in patients with COVID-19

The SARS-CoV2 infection has rapidly reached to a pandemic level, and due to its morbidity and mortality, has become a great worldwide concern. It is also indicated that older adults and those with obesity and/or underlying diseases such as diabetes and hypertension are more vulnerable to this infection (Guan et al., 2020; Li et al., 2020a; Yang et al., 2020; Zhang et al., 2020a). In a previ-

**Fig. 1. The role of diabetes mellitus in vulnerability to acute viral infections.** Both types of diabetes mellitus (T2D and T1D) are accompanied by hyperglycemia and obesity. Obesity, is defined by hypertrophy of adipose tissue that can lead to production of some pro-inflammatory mediators. This adipose tissue induced mediators, alongside with inflammation caused by hyperglycemia, can lead to altered immune profile that can put patients at higher risk of acute viral infections.

ous study among 1099 patients diagnosed with COVID-19, those who had comorbidities of hypertension (23.7%), diabetes melli-

tus (16.2%), coronary heart diseases (5.8%), and cerebrovascular diseases (CVD) (2.3%) represented much more disease severity,

compared to others (Guan et al., 2020). Moreover, hypertension and diabetes with incidence rates of 30% and 12%, respectively, were the most common comorbidities of COVID-19 patients admitted to a hospital (Zhang et al., 2020a). Among 191 COVID-19 patients who were included in a cohort study conducted in China, 91 patients had underlying diseases such as hypertension, diabetes and coronary heart disease, in order (Zhou et al., 2020). In this regard, the COVID-19 patients with cerebrovascular disease and diabetes comprised the majority of deceased cases from a group of 52 patients admitted to an intensive care unit (Yang et al., 2020).

Currently, the US is an epicenter of the COVID-19 pandemic. However, little data is currently available on a national level on the characteristics of patients, treatments, and outcomes of critical COVID-19 cases. A cohort study analyzed 2215 laboratory-confirmed COVID-19 adult cases, who were admitted to intensive care units (ICUs) at 65 hospitals across the US, in order to determine death-related factors and analyze the interhospital variations in treatment and outcomes. In specific, 1738 of the total patients (78.5%) had at least one coexisting condition, including hypertension (1322 [59.7%]), diabetes (861 [38.9%]), and chronic lung disease (531 [24.0%]). In this study, more than 1 in every 3 patients died within 28 days of admission to ICU. In specific, 824 (37.2%) were discharged from the hospital within 28 days, 784 (35.4%) died within this timeframe, and 607 (27.4%) remained in the hospital. Respiratory failure (727 [92.7%]), septic shock (311 [39.7%]), and kidney failure (295 [37.6%]) were the most prevalent causes of death, with multiple patients having more than 1 cause (Gupta et al., 2020b).

COVID-19 infection represents much more severity in those individuals with hypertension, diabetes, and coronary heart diseases. This severity can be contributed to the imbalance of ACE2 and cytokine storm mediated by Glucolipid metabolic disorder, as a condition associated with the neuroendocrine disorders, insulin resistance, oxidative stress, and chronic inflammatory responses (Chen et al., 2020d). According to the Chinese center of disease control report, COVID-19 patients with CVD, diabetes, and hypertension had the higher fatality rates (10.5%, 7.3% and 6%, respectively) compared to the overall fatality rate of 2.3% in COVID-19 patients without these comorbidities (Wu and McGoogan, 2020). It has also been confirmed that several factors may potentially worsen the prognosis of COVID-19 disease in the patients. Accordingly, old age, male sex, and diseases with high expression of ACE2 (such as CVD, hypertension, and diabetes) were identified to be associated with a poor prognosis of COVID-19 patients (Chen et al., 2020c; Giagulli et al., 2020).

SARS-CoV2 utilizes ACE2 for cell entry which is also used by SARS-CoV. However, the novel virus uses no dipeptidyl peptidase, which is a receptor used by MERS-CoV (Li et al., 2003; Raj et al., 2013). Also, ACE2 is expressed in lungs and extrapulmonary tissues including heart, kidneys, lung, and testis (Wan et al., 2020). In a study on eight different ethnical groups, 0.64% of lung cells were ACE2 positive, but surprisingly, among the Asian men, this rate was 2.5%. According to this evidence, Asians may be more vulnerable to COVID-19 compared to the other racial groups. Additionally, ACE2 expression levels are higher in men than women (Chen et al., 2020b; Li et al., 2020b).

Hypertension is suggested to cause pro-inflammatory actions through inducing the expression of several mediators, including chemokines, leukocyte adhesion molecules, specific growth factors, angiotensin, heat shock proteins and endothelin-1 (Bataillard et al., 1995; Bush et al., 2000; Clozel et al., 1991; Haller et al., 1995; Hilgers et al., 2000; Johnson et al., 1992; McCarron et al., 1994; Schmid-Schönbein et al., 1991). Furthermore, a direct association is reported between blood pressure reduction therapies and decreases in some of the circulating inflammatory markers (Li and Chen, 2005). Recent evidence also suggests an association between this immune process and the rennin-angiotensin system (RAS) (Pfab et al., 2007). The activation of RAS is often reflected by an increased level of Ang II. In addition to its role in the regulation of vascular tone, Ang II plays a determinant role in the inflammatory reactions. In hypertensive patients it is shown that the monocytes in the peripheral blood are pre-activated and thus produce elevated levels of IL-1b, due to Ang II stimulation, in comparison with the healthy controls (Dörffel et al., 1999). Ang II also induces the activation of NF-kB, which, in turn, induces MCP-1 and the synthesis of inflammatory cytokines, including TNF-$\alpha$ and IL-6 (Han et al., 1999; Li , 2005; Ruiz-Ortega et al., 2002).

The most of comorbidities in COVID-19 patients are strongly associated with the severity of the disease, and as mentioned earlier, the comorbidities are generally treated by ACE inhibitors, which induce ACE2 upregulation (Fang et al., 2020). Hypertension, T1D and T2D, as the most prevalent comorbidities, are treated by ARBs and ACE inhibitors, respectively (Wan et al., 2020). Because, these drugs can upregulate ACE2 expression (Li et al., 2017b). ACE2 hydrolyzes Ang1 and Ang2 to Ang1-9 and Ang1-7, respectively. Ang1-7 plays different protective roles such as anti-inflammatory, anti-hypertrophy, anti-cell proliferative and anti-fibrosis effects (Vaduganathan et al., 2020). Therefore, blunting the activity of Ang1-7 can induce inflammation and acute immune reactivity in the lungs (Touyz et al., 2020). The ACE2 upregulation induced by these drugs may facilitate the virus entry (Fang et al., 2020) (Fig. 2). Besides, these drugs are suggested to affect the severity and mortality of COVID-19 infection (Yang et al., 2020).

Although the consumption of RAS inhibitors may affect the expression of ACE2, which may theoretically increase the proliferation of SARS-CoV, some studies have shown that RAS inhibitors may change the expression of ACE2 in heart, kidneys, and plasma. However, it is still not clear whether ACE2 expression in airway epithelial cells is affected by RAS inhibitors. It should also be noted that in patients with high blood pressure, the expression of ACE2 is lower (Ferrario et al., 2005; Li et al., 2020b), and ACE inhibitors could have ameliorating effects on those who are at the risk of pneumonia or suffering from it. In a previous study, prescribing lipophilic ACE inhibitors led to a reduction in the fatality of patients with community-acquired pneumonia. In terms of treatment, these contradictions are of great importance, as ACE inhibitors can reduce the inflammation and may be considered as a potential novel therapy for inflammatory lung diseases, diabetes, hypertension and cancers (Mortensen et al., 2008). Susceptibility to SARS-CoV2 infection may also be attributed to ACE2 polymorphisms, since these genetic variations are related to diabetes mellitus, hypertension and cerebral stroke, which are particularly observed in the Asian population (Fang et al., 2020). Upon bind-
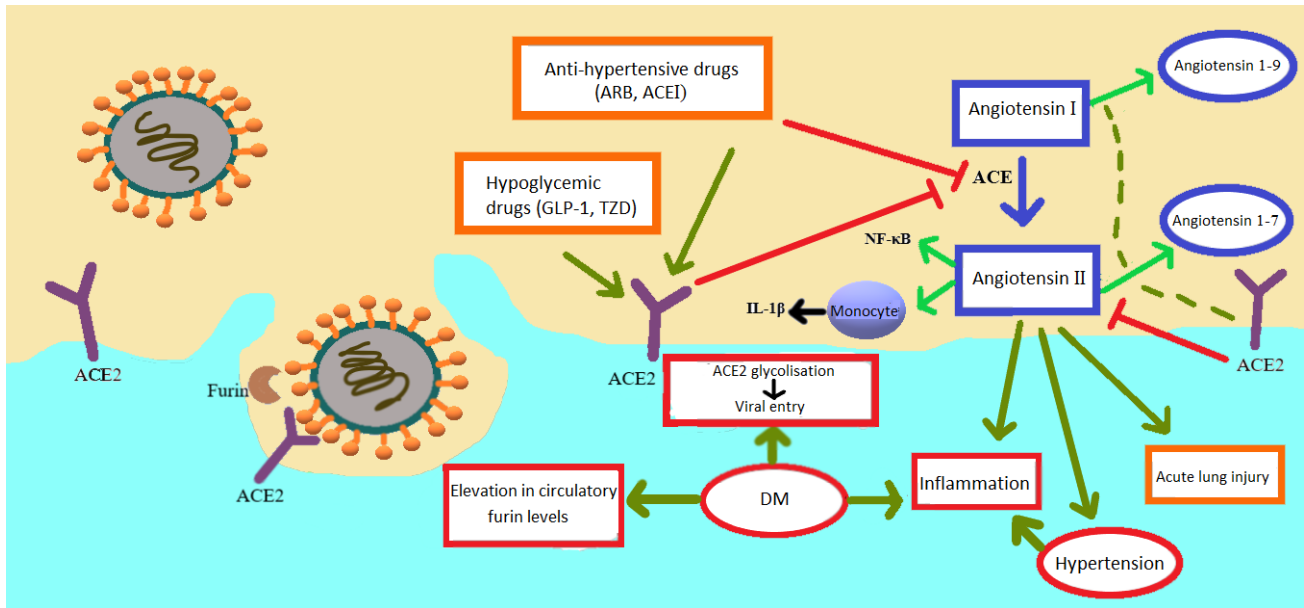
**Fig. 2. Angiotensin I is converted to angiotensin II by ACE enzyme.** Angiotensin II a vasoconstrictor agent causing hypertension, inflammation and acute lung injury. Moreover, angiotensin II induces the inflammatory pathway through activating NF$\kappa\beta$. It also stimulates monocytes to secrete IL-1$\beta$. ACE2, the receptor of SARS-COV2 converts angiotensin I and angiotensin II to angiotensin 1-9 and angiotensin 1-7, respectively. ACE2 also counter regulates ACE enzyme activation. Hypertension and diabetes induce an inflammatory state in the body. Furthermore, diabetes mellitus (DM) results in more ACE2 and spike protein glycosylation which helps viral entry. DM patients also have elevated levels of furin protease which cleavage spike protein and helps viral entry. Anti-hypertensive and hypoglycemic drugs that block the ACE enzyme pathway upregulate the expression of ACE2 and could facilitate virus entry.

ing of SARS-CoV to its cellular receptor ACE2, the virus results in ACE2 downregulation (Cui et al., 2019; Su et al., 2016). The binding of coronavirus to ACE2 alone induces no severe lung injury. However, downregulating ACE2, the level and activity of angiotensin II (Ang II) may increase, and as ACE2 level is insufficient to counter its activity, an acute lung injury may be happened. Besides, in a recent study in patients with COVID-19, Ang II levels were reported to be significantly increased, and to be positively associated to the level of lung injury and viral load (Guo et al., 2020a; Vaduganathan et al., 2020).However, it has not been fully understood so far whether SARS-CoV2 infection leads to the ACE2 downregulation. That is why that the American College of Cardiology and the American Society of Hypertension have suggested to the patients to keep taking their antihypertensive drugs. So, there may be beneficial effects in taking Ang II receptor blockers, TZDs, ACE inhibitors, statins and GLP-1 agonists in the context of low ACE2 expression (Danser et al., 2020; Muniyappa and Gubbi, 2020). Overall, there is currently no definite relationship between the susceptibility to COVID-19 and the use of RAS inhibitors (Li et al., 2020b).

In a study conducted among COVID-19 patients, the males, those with older age, and underlying diseases, such as hypertension, coronary heart disease, cardiomyopathy, and chronic kidney disease had high troponin T levels c TNT. The patients with high c TNT levels also had the increased levels of leukocyte count, prolactin, D-dimer, N-terminal pro-brain natriuretic peptides and C reactive protein, and a reduced level of lymphocyte counts (Guo et al., 2020b). The patients with such characteristics had an increased risk for developing severe complications, including acute respira-

tory distress syndrome, acute renal coagulopathy, acute lung injury and malignant arrhythmia. Besides, those with elevated TNT levels had the highest fatality rates, compared to those without such an elevation (Madjid et al., 2020).

D-dimer is developed from lysis and formation of cross-linked fibrins and reflects the activation of fibrinolysis and coagulation (Zhang et al., 2018, 2020b). It has been shown that COVID-19 was connected to hemostatic abnormalities. In specific, elevated D-dimer levels were seen in mortality cases (Connors and Levy, 2020; Zhou et al., 2020). Factors affiliated with mortality are high D-dimer, elevated IL-6, increased PT, and other biomarkers that indicate inflammation, high levels of troponin, and comorbidities such as coronary artery disease, old age, hypertension, and diabetes (Connors and Levy, 2020; Guan et al., 2020).

A study suggested that serum levels of Inflammation-related biomarkers, including serum ferritin, C-reactive protein, IL-6 and coagulation index, and D-dimer, were significantly higher ($P <$ 0.01) in patients with diabetes. This indicates that diabetic patients are more susceptible to inflammatory storms, and ultimately, rapid COVID-19 deterioration (Guo et al., 2020c). Moreover, new studies manifested a strong and independent connection between obesity and the severity of COVID-19, even in the absence of other co-morbidities (Lighter et al., 2020; Mosleh et al., 2020; Simonnet et al., 2020). Obesity can be defined as a chronic inflammatory condition linked with abnormal paracrine and endocrine activities of adipocyte-derived factors. Obesity can cause disarrangement in vascular homeostasis and can lead to endothelial disease. Even though the procedure that leads obesity to aggravate COVID-19 infections are not completely understood, endothelial diseases are

probably the necessary association (Engin, 2017; Korakas et al., 2020; Mosleh et al., 2020). Prothrombotic conditions are obvious in COVID-19 infected patients, along with stroke, high levels of D-dimer, deep venous and arterial thrombosis, microvascular and intracardiac thrombi, and pulmonary embolism. It is assumed that endothelial diseases and endotheliitis (the blood vessel wall inflammation) cause the formation of thrombus (Ciceri et al., 2020; Mosleh et al., 2020). Nevertheless, the prediction reliability and the ideal cutoff value for D-dimer to prognose mortality are not assessed properly (Tang et al., 2020; Zhang et al., 2020b).

Several studies have indicated that individuals with diabetes are at a greater risk for SARS-CoV2 infection, and developing severe complications like death (Bloomgarden, 2020; Hill et al., 2020). It is confirmed that diabetic patients are more vulnerable to infections, especially pneumonia and influenza. Nevertheless, good glycemic control is beneficial, which lowers the infection risk in these patients. Diabetic patients are generally more susceptible to be severely infected by viruses, especially respiratory ones (Gupta et al., 2020a). It has also been recently announced that viral clearance in the patients with COVID-19 is delayed (Iacobellis, 2020; Li et al., 2017a). A current study in Italy revealed that diabetic patients accounted for more than two-thirds of SARS-CoV2 death cases (Remuzzi and Remuzzi, 2020). Correspondingly, a Chinese report revealed that among the COVID-19 patients admitted to an intensive care unit, 48% had a comorbidity, within which hypertension was the most common comorbid disease (30%), followed by diabetes (19%) and coronary heart disease (8%). (Zhou et al., 2020).

Several mechanisms are suggested as the underlying reasons for why diabetic patients are prone to COVID-19 infection, including high-affinity cellular binding and effective virus entry, delayed viral clearance, decreased function of T cells, being more liable to inflammation and cytokine storm and CVD comorbidities (Muniyappa and Gubbi, 2020). Interestingly, having blood glucose of diabetic patients under control (maintaining blood glucose within the range of 3.9 to 10.0 mmol/L), adverse outcomes and mortality rate of the disease may be mitigated (Zhu et al., 2020). Also, in a non-obese diabetic (NOD) diabetic mouse model study, an increase was found in the ACE2 protein levels, compared to the control group, which was ameliorated following insulin treatment (Roca-Ho et al., 2017). Similarly, a recent study suggested that a reduction in glycosylated ACE2 in the lungs and consequent glycosylated viral binding sites may ameliorate COVID 19 symptoms, which suggests a paracrine loop theory. This theory implicates that infection of pancreas and lung with SARS-CoV2 may lead to a hyperglycemic state followed by the upregulation in glycosylated ACE2; hence, further virus binding and inflammation may occur (Brufsky and Lotze, 2020).

A theory suggests that the DC-SIGN (dendritic cell-specific ICAM-3-grabbing nonintegrin) and L-SIGN (DC-SIGNR, CD209L, or lymph / liver-specific SIGN) carbohydrate receptor is possibly a part of pathogenesis of the COVID-19 (Brufsky and Lotze, 2020). Dendritic cells (DC) express DC-SIGN. As a C-type lectin family membrane receptor, DC-SIGN is expressed on DCs with a primary role in identifying high mannose glycans found on pathogens or other cellular receptors (Garcia-Vallejo and van Kooyk, 2013). With the expression of L-SIGN, as the other

SIGN detected in humans (Gardner et al., 2003), both mannose receptors are implicated in virus capturing and entry into cells (Marzi et al., 2004). L-SIGN, which is expressed on type II alveolar cells of humans, is correlated with ACE2 (Jeffers et al., 2004) and may increase ACE2 mediated binding and cellular entrance of viral pseudotypes expressing the SARS-CoV spike protein S (Marzi et al., 2004). Lentiviral pseudotyped viruses that express SARS-CoV S protein need endosome acidification for viral entry (Yang et al., 2004). DC-SIGN mediates these pseudotyped vectors' binding to human DC with uptake into the endosome, followed by endosome polarization and virus delivery in an "infectious synapse" (Yang et al., 2004). De-glycosylation decreases the infectivity of viral pseudotypes that express SARS-CoV spike protein (Han et al., 2007). Specific asparagine glycosylation sites in three clusters within the SARS CoV S protein seem to be important for DC / L-SIGN, but not ACE2, mediated SARS Co-V pseudotype entry (Han et al., 2007). Infectivity mediated by DC / L-SIGN is decreased in proportion to the number of mutated glycosylated sites, showing that the glycosylated sites' number, and not just specific mutation, is significant (Han et al., 2007), which shows a mechanism for enhancement in viral virulence through increasing glycosylation of the SARS-CoV-2 spike (Brufsky and Lotze, 2020).

In T2D, as the most common type of diabetes, the excessive adipose tissue induces a mild chronic inflammatory status, which affects glucose regulation and insulin sensitivity. Also, Hyperglycemia and inflammation induced by diabetes result in a defective and inefficient immune system. Accordingly, this defective immunity is characterized by a diminished mobilization of polymorph nuclear leukocytes, chemotaxis and phagocytic activity. These changes are results of a decrease in inflammatory cytokine production in response to lipopolysaccharide, which is the prohibition of tumor necrosis factor-alpha activity by T cells and immunoglobulin glycation (Iacobellis, 2020). It has been announced that diabetes affects both arms of immunity. The innate immunity impairment is characterized by the inhibition in neutrophil chemotaxis, phagocytic activity and intracellular killing of microbes. Also, the adaptive immunity impairment can be identified by a delay in both Th1 cell activation and the hyperinflammatory process (Hodgson et al., 2015). Laboratory findings of the diabetic patients with COVID-19 revealed higher levels of neutrophil and leukocyte counts, fasting blood glucose, serum urea and creatinine and creatinine kinase isoenzyme MB, compared to those without diabetes on the point of admission. In another study, it was found that the SARS-CoV2 patients with underlying disease of diabetes presented much more severity of COVID-19 infection. These patients, compared to non-diabetic patients, developed more medical complications and higher incidence rates of antibiotic therapy, invasive and non-invasive mechanical ventilation and death. The COVID-19 patients also showed decreased levels of CD4 and CD8 Lymphocyte counts and increased levels in cytokine and proinflammatory T17 CD4 cells ratio (Guan et al., 2020; Wu and McGoogan, 2020; Xu et al., 2020; Yang et al., 2020; Zhang et al., 2020a).

ACE2 expression has been found to be increased in the lungs of patients with diabetes (Rao et al., 2020). In rodent models of DM, increasing in ACE2 expression was also observed iin the

lungs, heart, pancreas and kidney (Roca-Ho et al., 2017; Wysocki et al., 2006). ACE2 overexpression in diabetes can be modulated with insulin treatment (Roca-Ho et al., 2017; Wysocki et al., 2006). In contrary, the administration of hypoglycemic drugs such as glucagon-like peptide -1 (GLP-1) agonists (e.g., liraglutide) and thiazolidinediones (TZDs) (e.g., pioglitazone) may lead to the ACE2 upregulation. Moreover, ACE inhibitors can be used as antihypertensive drugs, as statins may induce ACE2 overexpression, as well (Ferrario et al., 2005; Romaní-Pérez et al., 2015; Tikoo et al., 2015; Wösten-van Asperen et al., 2011; Zhang et al., 2014). Furin is a protease involved in the cleavage process of the S1 and S2 domains of spike protein, and its circulating levels may be elevated in diabetic patients (Fernandez et al., 2018). This elevation can be considered as one of the reasons explaining the susceptibility of diabetic patients to SARS-CoV2 infection (Fig. 2). Diabetic patients are regularly on GLP-1 receptor agonists and/or Dipeptidyl peptidase-4 inhibitors (DPP4), as a class of oral hypoglycemic drugs. Also, the effect of DPP4 inhibitors on the immune system has not yet been fully known. It has been observed that DPP4 inhibition may not remarkably accelerate the risk of upper respiratory tract infection (Yang et al., 2016). However, several studies indicated the anti-inflammatory and anti-adipogenic effects of DPP4 and GLP-1 agonist administrations, respectively (Iacobellis, 2015). The anti-inflammatory effects of GLP-1 is mediated through decrease in macrophage infiltration (Iacobellis, 2020). A reduction in insulin resistance and M1/M2 macrophage polarization has also been associated with the inhibition of DPP4 and GLP-1 activation.

Furthermore, in a mouse model, ACE2 gene expression was reported to be increased by estrogen (Bornstein et al., 2020). Therefore, as men are at the higher risk for acquiring COVID-19 and having more disease severity than women, ACE2 may be suggested as a protective factor for SARS-CoV2 infection along with its pathogenicity. Recent studies have also reported that ACE2 gene expression was much higher in the tissues of younger adults and women, which is shown to has an inverse correlation with the disease severity (Chen et al., 2020a). Brufsky reported a possible explanation that the experiments of gene expression may not be capable of measuring the posttranslational modifications, including glycosylation of proteins (Brufsky and Lotze, 2020). Unlike the amount of ACE2 protein, ACE2 activity in the lungs was reported to neither rise nor fall by the insulin administration in the NOD diabetic mouse model (Roca-Ho et al., 2017). Since the antibody binding to proteins could be affected by glycosylation, as measured by Western blot analysis, the above-mentioned findings of the NOD diabetic mouse model study were consistent with an increase in glycosylated ACE2, as opposed to total ACE2 (Bass et al., 2017). Brufsky associated it to the amount of glycosylated ACE2 receptor, which is responsible for virus binding as well as fusion, not the amount of ACE2 alone. He also suggested a better glycemic control in pre-diabetic and diabetic patients as a potential mechanism to slow down the COVID-19 spread and to reduce the severity of symptoms, which may be regarded to the high A1c as a potential risk factor for COVID-19 (Brufsky and Lotze, 2020). Moreover, the patients with SARAS-CoV2 who have comorbidities of diabetes, hypertension and CVD should be under the observation of ACE2 modulating drugs. In this regard, to better clarify the mechanism involved in COVID-19 severity, a full description of the drugs consumed is required (Fang et al., 2020).

### 3.3 Diabetes mellitus and hypertension in the patients with MERS

The MERS-CoV epidemic appeared in Saudi Arabia in June 2012 (Mohd et al., 2016). The intermediate host of the virus were dromedary camels, from which the virus could be transmitted to humans via close contact. It was supposed that in the faraway past, the MERS-CoV was probably transmitted to dromedary camels from its origin, i.e. bats (Memish et al., 2020; Mohd et al., 2016). Up to November 30, 2019, a total number of 2494 laboratory-confirmed cases of MERS-CoV were reported. The virus resulted in 858 deaths (case-mortality rate: 34.4%) within 26 countries. The most of cases were from Saudi Arabia, including 2102 infection cases with a case-mortality rate of 37.1% (Madjid et al., 2020). Male sex, older age and underlying medical conditions such as cardiac diseases, diabetes mellitus, chronic kidney disease, hypertension, respiratory disease and cancers were identified as the clinical risk factors responsible for MERS mortality (Matsuyama et al., 2016; Park et al., 2018). A transmission study was performed in a single extended family, and indicated that, among the confirmed MERS-CoV positive members, there was more than 3 times higher possibility of suffering from a comorbid disease (Arwady et al., 2016). Another study reported that among 17 diabetic cases, 15 (88%) patients had poor outcome of the disease, including admission to intensive care unit and death. Meanwhile, only 7 out of 18 cases with comorbidities other than diabetes, had poor outcomes of the disease. It was concluded that diabetes, in particular, has significant effects on the severity of MERS-CoV disease (Garbati et al., 2016). However, due to the target populations and also the designs of the studies, there was a high heterogeneity within the risk levels related to the different comorbidities. In several studies, diabetes was indicated as an important risk factor leading to severe or fatal MERS disease. When a MERS patient has diabetes as comorbidity, the odds ratio of developing severe or fatal MERS disease is ranged from 2.47 to 7.24, depending on the target population and also on the design of the study (Alraddadi et al., 2016; Arwady et al., 2016; Banik et al., 2016; Choi et al., 2016).

A methodical analysis on 637 MERS-CoV cases showed the comorbidity of hypertension, cardiac diseases, obesity and diabetes to be 50%, 30%, 16% and 50%, respectively (Badawi and Ryoo, 2016). It is suggested that diabetes and conditions related to it may downregulate the humoral and innate immune systems by lowering the functions of neutrophils and T cells (Casqueiro et al., 2012). *In vitro* (*laboratory*), hyperglycemia damages critical components of innate immunity, including phagocytosis, chemotaxis and the bactericidal activity of macrophages and neutrophils, which may cause secondary infections (Benfield et al., 2007). A study by ((Badawi et al.)) also showed an etiological relationship between diabetes and acute viral respiratory infections. However, the direct effect of diabetes on severe respiratory infections still requires more investigations. The rate of diabetes under acute viral conditions should be evaluated to clarify the etiologic role of diabetes in case of infection seriousness (Garcia et al., 2012). ((Kulcsar et al.)) in a study used expression of human DPP4 to make mice susceptible to MERS-CoV, and applied a diet with a high-fat amount to induce them to T2D (Kulcsar et al., 2019). Being in-

fected by MERS-CoV, mice that had diabetes showed a long phase of acute disease and late recovery, which were not depended on the virus titers. Their analysis demonstrated that the mice with diabetes developed delayed inflammation prolonged to 21 days since infection. The mice with diabetes had less inflammatory monocytes and macrophages. They also had fewer CD4 positive T cells, which was associated with fewer amounts of the expressions of *Cxcl10* and *Ccl2*. In addition, the mice with diabetes had higher amounts of expressing *Il17α* and lower amounts of the expressions of *Il12b*, *Tnfα*, *Arg1*, and *Il6*. All these findings suggest that the higher disease severity in MERS cases with T2D, as comorbidity, is probably due to their deregulated immune response, which may lead to more acute and prolonged lung pathology.

### 3.4 Diabetes mellitus and hypertension in patients with SARS

Several studies on individuals suspected to pass out due to SARS-CoV infection have evidenced some atypical pathological changes, including fatty degeneration, hydropic degeneration and interstitial cell affecting the pancreas, kidney and heart (Shi et al., 2005). SARS-CoV may lead to CVDs, as well. In addition, myocardial infarction and the acute coronary syndrome were reported to occur following the SARS infection (Chong et al., 2004; Peiris et al., 2003). In a small cohort study on 75 hospitalized patients diagnosed with SARS, acute myocardial infarction (AMI) was reported to cause death in 2 out of 5 fatal cases (Peiris et al., 2003). In a study among 121 individuals infected by SARS-CoV, a majority of the patients (79.3%) had a good health history and only 20.7% (25 cases) had concurrent medical problems, including hypertension (n = 7), asthma (n = 4), diabetes mellitus (n = 5), old pulmonary tuberculosis (n = 1), valvular heart disease (n = 2), chronic renal failure (n = 2), CVD (n = 1), bronchiectasis (n = 1), and stroke (n = 2). These patients were managed based on the guidelines (Ho, 2003; Yu et al., 2006).

Based on the results of a previous study among patients with SARS , having diabetes and/or other comorbidities (including cancers, CVD and chronic obstructive pulmonary disease) were correlated with a composite risk of intubation, death and the need for admission to an intensive care unit (Dodek, 2004). In another previous study, even mild SARS cases who received no glucocorticoid medicines during the study had higher levels of fasting plasma glucose (FPG), suggesting that hyperglycemia may be an independent death predictor, within (Yang et al., 2006). During follow-up, they also found that diabetes occurred during the hospitalization of 20 out of 39 individuals who received no corticosteroids throughout the SARS course. Additionally, diabetes was reported in two of the patients after 3 years of follow-up. Among the SARS-CoV infected individuals and their paired, healthy non- SARS-CoV infected siblings there were similarities in the rates of FPG, postprandial plasma glucose (PPG) and insulin even 3 years after follow-up, which indicated the temporary damage of SARS-CoV to islets.

The researchers' retrospective analyses showed that a history of ambient hyperglycemia and diabetes prior to initiation of steroid therapy were two independent risk factors for higher mortality and morbidity rates. This study was the first study that showed the high fatality rate of diabetic individuals experiencing SARS-CoV infection. Since then, there have been a growing number of studies demonstrating the enhanced rates of morbidity and mortality among diabetic individuals hospitalized with various severe medical conditions, such as myocardial infarction, despite the independent predictive role of the high FPG levels among hospitalized nondiabetic patients (Umpierrez et al., 2002; Van den Berghe et al., 2001, 2003). The diabetogenic effects of steroid drugs are also recorded. A previous study (Xiao et al., 2004) has demonstrated that 33 (34.7%) out of 95 SARS patients treated by steroids, experienced steroid-induced diabetes. These results, altogether, provide the evidence that hyperglycemia may increase the severity of viral infections, mortality rates and the risk of severe hypoxia among diabetic patients experiencing SARS. Insulin therapy and intensive monitoring to achieve an appropriate metabolic control may enhance the SARS patients' outcomes, which may be due to the potentially damaging effects of ketosis and hyperglycemia on the organs' function (Yang et al., 2006).

It was indicated that the binding of SARS-CoV spike (S) protein to its target cells' cellular receptor may mediate the SARS-CoV infection (Li et al., 2003; Turner et al., 2004b; Yang et al., 2010). Considering the extensive usage of ACE inhibitors (ACEIs) for the treatment of cardiovascular diseases such as hypertension, there was an interest in ACE2, as a possible treatment. This possibility was highlighted with the relatively high ACE2 expression's level in kidney and heart (Donoghue et al., 2000; Tipnis et al., 2000). Despite its close resemblance to ACE and the maintenance of several important active site characteristics, ACE2 showed a distinctive choice as substrates, which may particularly function as carboxypeptidase that eliminates single amino acids, unlike ACE that eliminates dipeptides from a peptide's C-terminus (Donoghue et al., 2000; Tipnis et al., 2000; Turner et al., 2004b). Additionally, evidence shows that ACE2 acts as a functional receptor for the S protein of SARS-CoV (Li et al., 2003; Turner et al., 2004b). A study conducted on the location of ACE2 protein in 15 human organs showed that ACE2 was plentiful in the small intestine and lung epithelia, where SARS-CoV could enter (Hamming et al., 2004). Another study (Harmer et al., 2002) on 72 human tissues evidenced the expression of ACE2 mRNA in testis, lung parenchyma, bronchus and gastrointestinal, renal and cardiovascular tissues, and pancreas, as well.

The most serious type of acute lung injury is known to be acute respiratory distress syndrome (ARDS). ARDS, as a clinical disease with high mortality rate, is mostly caused by an elevated rates of permeability in pulmonary vessels and pulmonary edema, which is often induced by coughing, sepsis and pneumonia (such as those caused by human influenza, bird flu, and SARS viruses) (Lin et al., 2020). As mentioned earlier, ACE, as an important enzyme in RAS, transforms angiotensin (Ang) I to the vasoconstrictor Ang II. Accordingly, Ang II is believed to cause the most of RAS' pathophysiological and physiological effects. This typical conception of the RAS was questioned after the discovery of the ACE2 enzyme, which diminishes Ang II and takes part in the production of the antiproliferative and vasodilatory peptide, Ang 1-7 (Dean and Burrell, 2007). Extremely expressed in lung, ACE2was proved to have protective effects in acute lung injury (Imai et al., 2005; Lin et al., 2020). Lung tissue has an extreme activity in the RAS and is the leading site for Ang II synthesis. Ang II is also known as an important pulmonary vasoconstrictor. Notably is that during hypoxia, RAS is triggered. In this regard, Ang II may

not only promote the growth response of vascular smooth muscle cells, but may also elevate directly the vascular remodeling and avoid pneumonia and the shunts associated with lung injury (Kiely et al., 1997). However, Ang II can also enhance the development of pulmonary edema and hinder the lung's function (Imai et al., 2005). It is currently understood that the impact of RAS inhibitors on ACE2 is largely due to the ACE2 expression in the plasma, kidney and heart (Li et al., 2020a). ACE2 expression has also indirect associations with hypertension. It was also reported that (Crackower et al., 2002) among rats, the gene maps of ACE2 to a defined quantitative trait locus had an association with hypertension. Besides, two single nucleotide polymorphisms in ACE2 gene locus had an association with human CVD (Turner et al., 2004a). Furthermore, in streptozotocin-induced diabetes among rats, protein and renal tubule ACE2 mRNA expression have considerably decreased, but the expression of ACE2 protein increased in diabetic glomeruli (Tikellis et al., 2003; Turner et al., 2004b).

Up to now, there is no proof that the use of RAS inhibitors can cause patients to be more susceptible to the virus. Nonetheless, a previous study reported that treatment with an ACEI may degrade the ACE2 expression, but with no considerable impact on its activity (Ferrario et al., 2005).

## 4. Conclusions

Diabetes may downregulate the humoral and innate immune systems through reducing the functions of neutrophils and T cells, which may result in secondary infections. Similarly, hypertension was found in association with several comorbidities, which can increase the risk and severity of infectious diseases. That is why that the individuals with diabetes mellitus and hypertension are reported to be at higher risks for the late viral clearance of the coronavirus, and the worsened prognosis in SARS, MERS and COVID-19 infections. In SARS and COVID-19, this may also be due to the association of the comorbidities with higher levels of ACE2expression. It is also hypothesized that virus binding and fusion are also due to the amount of glycosylated ACE2 receptor and not the amount of ACE2, alone. Therefore, better glycemic control in pre-diabetic and diabetic patients is suggested as a potential mechanism to slow down the COVID-19 spread, besides reducing the severity of its symptoms. Furthermore, the control of blood pressure and lipids should be carried out in the T2DM patients. There is a need for careful consideration on the usage of ACE inhibitors in diabetes, hypertension, COVID-19 and SARS patients. Furthermore, diabetes and hypertension are considered comorbidities and these patients with COVID-19 should receive early outpatient treatment according to a multi-drug algorithm (McCullough et al., 2020). More information regarding the profile of hazards in the hospitalized SARS-CoV2 patients can be helpful in personalized treatments and better decision-making for this vulnerable population.

## Abbreviations

2019 Novel Coronavirus Disease: COVID-19; Middle East Respiratory Syndrome: MERS; Severe Acute Respiratory Syndrome: SARS; Angiotensin-Converting Enzyme 2: ACE2; Angiotensin II type-I Receptor Blockers: ARBs; Cardio Vascular Disease: CVD; Type 1 Diabetes: T1D; Type 2 Diabetes: T2D; T helper 1: Th1; T helper 17: Th17; Renin-Angiotensin: RAS; Acute Respiratory Distress Syndrome: ARDS; Glucagon-Like Peptide - 1: GLP-1; Thiazolidinediones: TZDs; Acute Myocardial Infarction: AMI.

## Authors' Contributions

Niloofar Deravi: Constructed the idea of manuscript- Supervised the course of the article- Co-wrote the manuscript- Critically revised the manuscript; Mobina Fathi: Co-wrote the manuscript - Did the data collection - Critically revised the manuscript; Kimia Vakili: Co-wrote the manuscript - Did the data collection - Critically revised the manuscript; Shirin Yaghoobpoor: Co-wrote the manuscript - Did the data collection- Critically revised the manuscript; Marzieh Pirzadeh: Co-wrote the manuscript - Did the literature review - Critically revised the manuscript; Melika Mokhtari: Did the literature review- Co-wrote the manuscript- Critically revised the manuscript; Tara Fazel: Co-wrote the manuscript- Critically revised the manuscript; Elahe Ahsan: Co-wrote the manuscript- Critically revised the manuscript; Samad Ghaffari: Supervised the course of the article- Critically revised the manuscript- Constructed the idea of manuscript.

## Conflicts of Interest

The authors declare they have no conflicts of interest.

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