

## Review Article

# Diabetes mellitus augments the complications of patients with COVID-19: a review

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### ABSTRACT

Corona virus disease 2019 (COVID-19) is current pandemic infection caused by RNA virus named severe acute respiratory syndrome coronavirus-2 (SARS Cov-2). The lungs are the organs most affected by COVID-19 and people were died due to severe acute respiratory s syndrome, pneumonia and multi-organs failure. Fatality rate was more, those who suffer in chronic diseases including diabetes mellitus (DM). As COVID-19 pandemic is accelerating , it is important to understand the molecular mechanism through which DM increases the severity related to COVID-19 to able to design more appropriate therapy. The aims of this study was to identify mechanisms through re-analysis of publicly available data by which DM increases susceptibility for COVID-19 infection and/or increase complication for SARS-Cov-2 infection. SARS Cov-2 accesses host cells via membrane bound enzyme, angiotensin converting enzyme-2 (ACE2). This leads to imbalance of vasoprotective and vasodeleterious arms of renin angiotensin system (RAS) with over activity of vasodeleterious arms. Such imbalance of RAS induces alveolar damage, flooding the alveoli and difficulty in breathing. DM augmented the chance of pulmonary infection by impairment of innate immunity and down regulation of ACE2. Hence, diabetic patients of COVID-19 die from multi-organ failure, shock, heart failure, arrhythmias and renal failure along with severe acute respiratory syndrome. Thus it is concluded that DM augments the complications from COVID-19 by enhancing development of RAS imbalance. From view point of public health it is suggested to keep the lung healthy, maintain blood glucose level properly, and intake foods rich in antioxidant and anti-inflammatory agents to prevent and ameliorate the acute effect of COVID-19 in diabetic patients.

**Keywords:** Angiotensin converting enzyme, Antioxidant, COVID-19, Diabetes mellitus, Renin angiotensin system

### INTRODUCTION

Corona virus disease 2019 (COVID-19) is current pandemic infection caused by RNA virus named severe acute respiratory syndrome coronavirus-2 (SARS Cov-2). The disease was first observed in December 2019 in Wuhan, China and since then spread globally. WHO declared the 2019-2020 coronavirus outbreak a public health emergency of International concerned on 30th January 2020 and a pandemic on 11th March 2020.<sup>1,2</sup> More than 200 countries of the world now suffer in

COVID-19.<sup>3</sup> More than 1.2 million people are corona infected and more than 70,000 are died as on 6th April 2020, mainly from viral pneumonia and multi-organ failure.<sup>4,5</sup> At present (22nd April, 2020) more than 2.5 million people are infected and more than 0.17 million people were died in COVID-19 worldwide. Older patients with comorbid conditions including diabetes and hypertension have been associated with higher mortality rate.<sup>6</sup> Diabetes mellitus (DM) is a worldwide epidemic and considered as seventh leading cause of death.<sup>7</sup> DM is a risk factors for coronary artery disease, heart failure and

cerebrovascular disease. According to WHO, the prevalence of DM in adults was estimated to be 4% in 1995 and is predicted to rise to 5.4% by the year 2025.<sup>8</sup> The International Diabetes Federation (IDF) reported that the worldwide total number of people with diabetes will rise from 366 million in 2011 to 552 million by the year 2030 or one in 10 adults will have DM.<sup>9</sup> Prevalence of DM in India is very high and India will be considered as diabetic capital of the world from 2025.<sup>10</sup> In addition to the well-recognized complications and co-morbidities DM patients also suffer from decreased lung function and impaired immune function.<sup>11-13</sup> Diabetic patients are more likely to suffer from infection and at a greater risk of complications after infection.<sup>14,15</sup> In diabetic animal infection show diminished innate immunity at the site of infection and reduced circulating polymorph nuclear leukocytes function. Pulmonary infections are a common and significant threat to patients with DM.<sup>16</sup>

A recent study in China suggested that 22% diabetic patients have died in COVID-19.<sup>17</sup> In another study 16.2% confirmed COVID-19 patients are diabetic.<sup>18</sup> This review article will put emphasis on the risk of corona infection and fatality from COVID-19 among diabetic patients. However, a focus of the article will be on pathophysiology of SARS-Cov-2 infection in diabetic subjects.

**REVIEW OF LITERATURE**

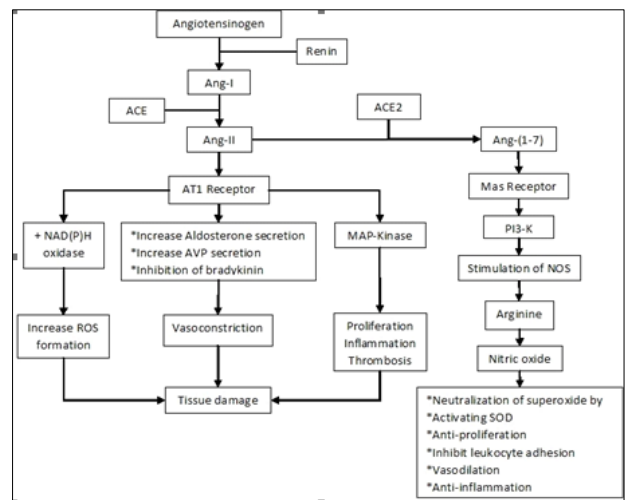
**Coronavirus**

Corona viruses are enveloped no segmented positive sense RNA viruses. They belong to the family Coronaviridae and the order Nidovirales.<sup>19</sup> Two type corona viruses' viz. severe acute respiratory syndrome corona virus (SARS-Cov).<sup>20,21</sup> And Middle East respiratory syndrome corona virus (MERS-Cov) are epidemic.<sup>22,23</sup> Severe acute respiratory syndrome coronavirus-2 (SARS Cov-2) is a novel severe acute respiratory syndrome coronavirus, first isolated in people in Wuhan, China in those who suffer from pneumonia connected to the acute respiratory illness. SARS-Cov-2 is closely related to the original SARS- Cov.<sup>24</sup> This virus is mainly spread during close contact and by small droplets produced cough, sneeze, talk and expired air of infected person. People may also infected by touching contaminated surface and then their face. The lungs are mostly affected by COVID-19 because virus accesses host cells via membrane bound enzyme ACE2 in the type-II alveolar epithelial cells.

**Pathophysiology**

Lung epithelial cells express high level of ACE2.<sup>25,26</sup> In SARS-Cov and SARS-Cov2 induced cute respiratory syndrome (ARDS) involvement of ACE2 was established in multiple animal models.<sup>27</sup> ACE2 knock out mice exhibit severe pathology of ARDS.<sup>28</sup> Treatment with ART1 blocker of ACE2 knock out mice rescues from

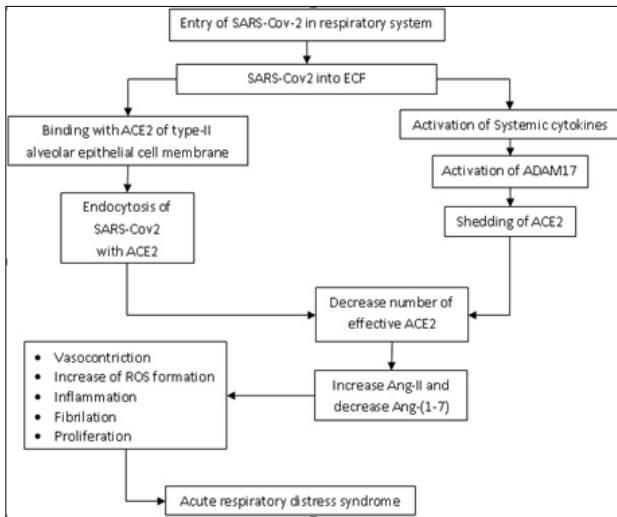
ARDS. SARS-Cov and SARS-Cov-2 bind to their target cells through angiotensin converting enzyme-2 (ACE2) by their surface glycoprotein called spike and then enter into target cell by endocytosis.<sup>29,30</sup> ACE2 is abundant in the type-II alveolar epithelial cells of the lungs. This supports that the lungs are the organ most affected by COVID-19. Type II alveolar epithelial cells secrete lung surfactant which keep the lungs fluid and clean. Renin angiotensin system (RAS) is a cascade of vasoactive peptides involve in the maintenance of blood pressure homeostasis. This system consists of two principal enzymes viz ACE and ACE2. ACE cleaves decapeptide, angiotensin-I to octapeptide angiotensin-II. ACE- 2, carboxy peptidase, is a 42% homologue of ACE and captopril insensitive carboxypeptidase.<sup>31,32</sup> It cleaves carboxy terminal peptide bond of angiotensin-I and angiotensin-II and produces Ang-(1-9) and Ang-(1-7).<sup>32</sup> Catalytic efficiency of ACE2 against Ang-II is remarkably higher than Ang-I.<sup>33</sup> Thus ACE2 is the main enzyme for Ang-(1-7) generation in many tissues.<sup>34</sup> Thus in RAS there are two angiotensin converting enzymes (ACE and ACE2) and two mediators (Ang-II and Ang-1-7) and performs dual function: vasoconstrictor/proliferative or vasodilator/antiproliferative actions depending on ACE/ACE2 balance.<sup>35,36</sup> According to this concept elevated ACE activity is associated with reduced ACE2, increase Ang-II formation and increase Ang-(1-7) catabolism leading to vasoconstriction, while in reverse condition there is vasodilation from increase ACE2, decrease ACE, decrease Ang-II and increase Ang-(1-7). There are two type of G-protein couple membrane bound receptor viz type-1 (AT1) and type-2 (AT2) for angiotensin peptides. AT1 receptor is associated with growth, inflammation and vasoconstriction while AT2 receptor is associated with opposite functions.<sup>37</sup> Ang-II exerts several cytokines like action via AT1 receptor and promote the formation of reactive oxygen species and other proinflammatory responses.<sup>38</sup> ACE2 acts via mas receptor (Figure 1).



**Figure 1: Novel components of renin-angiotensin system and their roles.**

Pulmonary edema in acute respiratory distress syndrome arise from increased hydrostatic pressure (due to pulmonary vasoconstriction) and/or increased microvascular permeability.<sup>39</sup> Increase pulmonary vascular permeability is a principal marker of acute lung injury.<sup>40</sup> Loss of ACE2 expression in acute lung injury leads to leaky pulmonary blood vessels through AT1 receptor stimulation.

Thus ACE-2 not only allows entry of SARS-CoV-2 into target cell but also down regulate its own expression. This indirectly increases activity of Agn-II which may be impart responsible for organ injury in covid-19.<sup>41</sup> After binding of SARS-CoV-2 with membrane bound ACE2 there is decrease number of membrane bound ACE2. Down regulation of ACE2 activity in lungs facilitates neutrophil infiltration in response to bacterial endotoxin from unopposed local RAS activation and Agn-II accumulation.<sup>42</sup> In a study with In COVID-19 patient's elevated plasma Agn-II was observed which is correlated with total viral load and degree of lung injury. Restoration of ACE2 through the administration of recombinant ACE2 reverse this devastative lung injury.<sup>43,44</sup> In the pathogenesis lung injury Ang-II is upregulated by ACE and causes severe lung failure through AT1receptor. On the other hand ACE2 and Mas receptor protect against lung injury. ACE2 gene is located in X-chromosome.<sup>45</sup> Hence expression of ACE2 will be more in female than male. This is may be one of the reason of less severity of COVID-19 in female than males.<sup>46</sup> Age related loss of ACE2 in the lungs correlated with the increased mortality and severity of ARDS in elderly patients with coronavirus (Figure 2).<sup>47</sup>



**Figure 2: Pathophysiology of SARS-Cov2-induced acute respiratory distress syndrome.**

From the above discussion it is suggested that acute lung injury is the impact of imbalance in the RAS as it is associated with: i).decrease pulmonary ACE2 ii). Increase pulmonary Ang-II iii). Supplementation with ACE2 or inhibition of Ang-II improves lung injury iv).

Lack or decrease of pulmonary ACE2 aggravate viral-induced lung injury.

**Diabetes mellitus and pulmonary infection**

Type-2 diabetes mellitus seems to be a risk factor for acquiring new corona virus infection.<sup>48</sup> Pulmonary infections are a common threat to patients suffering with diabetes. In DM a combination of an impaired immune system and tissue damage increases the chance of severe complication.<sup>49</sup> Diminished innate immunity causes uncontrolled bacterial growth leading to pneumonia.<sup>50</sup> DM is significantly associated with hypertension, nephropathy, retinopathy and cardiovascular diseases. Local RAS has been found in the various tissues including heart, blood vessels, kidney and pancreas.<sup>51</sup> RAS inhibitors significantly reduce the incidence complication in heart and kidney of DM patients and also reduces novel DM onset in hypertensive patients.<sup>52</sup> In the respiratory system ACE2 produces Ang-(1-7) by proteolysis of Ang-II. When ACE activity is increased and ACE2 activity is decreased Ang-II level is increased produces vasoconstriction and pro-inflammatory responses via AT1 receptor. On the other hand increase activity of ACE2 causes formation of Ang1-7 which produces anti-inflammatory responses and anti-fibrotic responses via Mas receptor that will be favorable to the recovery of patients with COVID-19.<sup>53</sup>

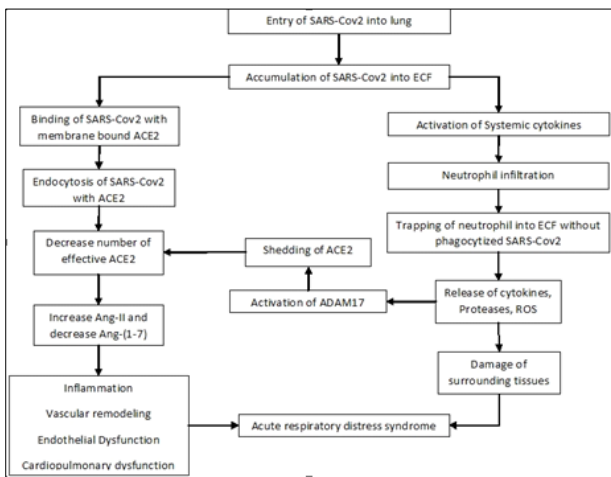
RAS plays vital role in vascular system. It has two arms: Vasodeleterious arm (which causes vasoconstriction, proliferation, fibrosis and inflammation via ACE-Ang-II-AT1 receptor) and vasoprotective arm (which mediates vasodilation, anti-proliferation and anti-inflammation through activation of ACE2-Ang-(1-7)-mas receptor). Vasoprotective effect of Ang-(1-7) involve decrease ROS production by inhibition of NADPH oxidase via the mas receptor and stimulation of nitric oxide production.<sup>54</sup>

Ang-(1-7) activates endothelial nitric oxide synthase (eNOS) through an Akt-dependent mechanism.<sup>55</sup> eNOS is a dimer made up of two identical monomers constituted by a reductase and oxidase domain. Reductase domain has binding sites for NADPH, FMN and FAD whereas oxidase domain contains binding sites for heme group, zinc and tetra hydro biopterin (BH4).<sup>56</sup> eNOS produces NO from arginine in presence of NADPH and oxygen. Molecular oxygen binds with heme group of eNOS.<sup>57</sup> BH4 is essential for formation of NO efficiently. In absence of BH4 dimeric eNOS becomes monomeric i.e. uncoupled. Uncoupled eNOS produces superoxide anion. eNOS has a protective function in the vasculature by increasing formation of nitric oxide (NO). NO diffuses across the vascular smooth muscle cell membrane and activates the soluble guanylate cyclase, which catalyzes the conversion of GTP to cyclic GMP. Cyclic GMP activates protein kinase-G (PKG) which in turn phosphorylates target proteins that decreases cellular Ca<sub>2</sub> promotes vascular relaxation.<sup>58</sup> NO exerts anti-proliferative effects indirectly via cyclic GMP mediated

inhibiting Ca<sub>2</sub> influx or by direct inhibition of activity of arginase and ornithine decarboxylase to decrease formation of polyamides which is required for DNA synthesis.<sup>59</sup> NO also has anti-oxidant properties as it reduces super oxide anion by increasing the expression of super oxide dismutase that catalyzes conversion of super oxide to hydrogen peroxide.<sup>60</sup> NO-dependent signaling plays a vital role in the mobilization of progenitor cells from bone marrow to area of vascular injury and re-endothelization.<sup>61,62</sup> Beside above function NO inhibit leukocytes adhesion on endothelial cell membrane.<sup>63</sup>

In diabetes nitric oxide bioavailability is decreased either from decreased eNOS activity or increased ROS production via upregulated NADPH oxidase.<sup>64</sup> In this condition NO reacts with super oxide anion to form peoxynitrite. Peoxynitrate oxidizes BF4 to BF3 and BF2 and causes uncoupling of eNOS. In this conformation eNOS produces superoxide anion instead of NO. Thus vascular injury in DM may be due to inhibition of ACE2.

Neutrophils Play critical role in the pathogenesis of ARDS. DM induces infiltration of neutrophil.<sup>65</sup> Activated neutrophil releases harmful mediators including, ROS and matrix metalloproteinase leading to tissue damage.<sup>66</sup> Certain cytokines like IL1, IL6 and IL8 and tumor necrosis factor are proinflammatory and induces lung injury.<sup>67</sup> Hyperglycemia induces neutrophil extracellular traps formation. Thus ROS was increased in extracellular environment in diabetes mice.<sup>68</sup> In diabetes rat treated with Ang-(1-7) ROS and other various cytokines (released by neutrophil) were increased in the intracellular compartments.<sup>69</sup> Thus increased extracellular ROS production is responsible for more tissue damage in diabetic patients (Figure 3).<sup>70</sup>



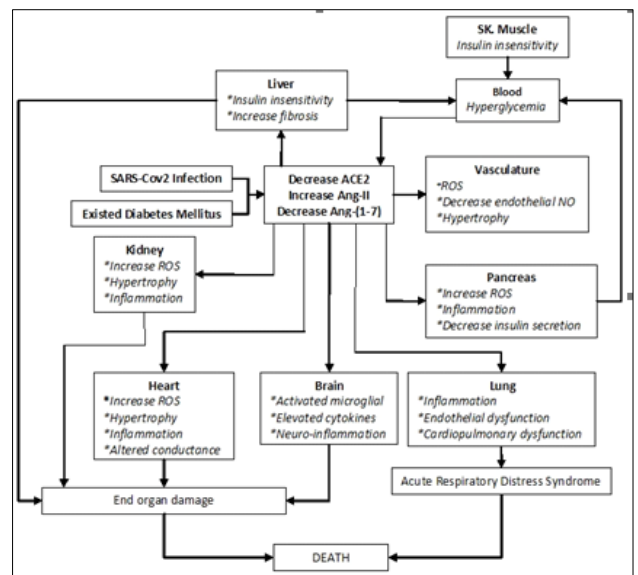
**Figure 3: Mechanism of diabetes-induced pulmonary infection.**

**DISCUSSION**

Hyperglycemia and DM are independent predictors of mortality and morbidity in patients with SARS.<sup>71</sup> In

COVID-19 there is imbalance between vaso-deleterious arm (which causes vasoconstriction, proliferation, fibrosis and inflammation via ACE-Ang-II-AT1 receptor) and vaso-protective arm (which mediates vasodilation, anti-proliferation and anti-inflammation through activation of ACE2-Ang-(1-7)-mas receptor) with an increase activity of vasodeleterious arm. SARS-Cov-2-induced increase activity vasodeleterious arm of RAS is due to decrease number of membrane bound ACE-2. Like SARS-Cov-2 in DM there is increased activity vasodeleterious arm of RAS. Combination of corona virus infection and type-2 DM trigger a dysregulated immune response, resulting in more aggravated and prolong lung pathology.<sup>72</sup>

Target of both SARS-Cov-2 and DM is RAS. Such system are distributed in various tissues including Lung, liver, kidney, heart, vasculatures, pancreas and brain.<sup>73</sup> DM-induced myopathy, neuropathy, and nephropathy is mainly due to imbalance of RAS. Many of the COVID-19 older patients with cardiovascular disease, liver disease or kidney disease become, severely ill.<sup>74</sup> COVID-19 particularly in diabetic subjects not only causing pneumonia may also cause damage to other organs such as heart, the kidney, the liver, the pancreas and the immune system.<sup>75,76</sup> Type-2 DM can contribute to multi organ failure in SARS-Cov infections as it induces imbalance of RAS in other tissues including lung, liver and heart.<sup>77</sup> Patients die from multi-organ failure, shock, heart failure, arrhythmias and renal failure (Figure 4).<sup>78</sup> Thus type-2 DM now considered as risk factor for acquiring new coronavirus infection.



**Figure 4: COVID-19-induce multi-organs failure and its augmentation by diabetes mellitus.**

**CONCLUSION**

Severe acute respiratory syndrome is most important clinical symptom of COVID-19. It arises from increased

vascular permeability, alveolar flooding, injury of type-I alveolar epithelial cells, infection of type-2 epithelial cells, hampered surfactant synthesis and increased alveolar surface tension and alveolar collapse. Such pathological changes in lungs is due to inflammation and tissue damage from increased formation of inflammatory cytokines and reactive oxygen species. COVID-19-induced pathology arises from impaired innate immunity and imbalance of RAS (Decrease ACE-2, increase Ang-II and decrease Ang-1-7) with over activity of vasodeleterious arm. DM augmented pathology of coronavirus infection by affecting innate immunity and RAS like COVID-19. From re-analysis of publicly available data it is concluded that DM augments the vulnerability from COVID-19.

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