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Review Article

Covid and Diabetes: A Literature Review

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Abstract

In December 2019, the WHO China Country office was informed of an outbreak of pneumonia of unknown etiology, in Wuhan city. The pathogen was later identified as a member of the β-coronaviridae family, and the disease it caused was named Covid-19. The outbreak rapidly evolved over the next few months to become a pandemic that resulted in drastic effects on global healthcare and economy. Diabetic patients were affected equally as non-diabetic individuals; however, the impact of the disease was much worse amongst them. We aim to briefly review the incidence and characteristics of Covid-19 infection among diabetic patients, elaborating into the pathophysiology of the disease and the possible mechanisms which may explain the severity of the disease amongst them, through a review of published articles in Pubmed, Google Scholar and Cochrane databases, till the first of January 2022.

Keywords: SARS-COV-2, Covid-19, incidence, diabetes, obesity, infection, treatment, immunity.

BACKGROUND

In December 2019, a cluster of cases with unusual pneumonia emerged in a business market in Wuhan, China. The WHO China country office was informed, the market was isolated, and investigations to identify the pathogen began [1].

Nine days later, the pathogen was identified as a member of the β-group of Coronaviridae family, in the Nidovirales order, which are single stranded RNA viruses. This novel virus was named SARS-COV-2 (Severe Acute Respiratory Syndrome Virus 2), and the disease it caused was named Covid-19 [2].

This is not the first time Coronaviridae spread panic in the world. In 2002, Severe Acute Respiratory Syndrome Virus (SARS-COV), also a member of the same Coronavirus family, caused an outbreak in Guangdong, China, resulting in more than 8000 infected persons in 26 countries, with a mortality rate of 9% [3]. Few years later, the Middle East Respiratory syndrome Coronavirus (MERS-COV) was responsible for an endemic in the Middle Eastern countries [4]. MERS-Cov resulted in more than 2428 cases of confirmed infections, and a mortality rate of about 34.5%. Patients affected by SARS-COV or MERS-COV typically present initially with symptoms of upper respiratory tract infection, which later progress to severe respiratory disease followed by acute respiratory distress syndrome (ARDS) and renal failure [5].

SARS-COV-2 infected patients typically present with symptoms of upper respiratory tract infection, as its predecessors, which may later progress to severe pulmonary symptoms, and, in occasions, cytotoxic storm characterized by the massive release of cytotoxic cytokines and markedly raised inflammatory markers. The transmission rate is higher than SARS-COV due to a genetic recombination event at S protein in the Receptor Binding Domain (RBD) region, however the mortality rate is much lower, varying (according to viral mutations that emerge) from 1.34 to 2.9% till the date of writing (although in a meta-analysis of 212 published articles it reaches as high as 6%) [1, 6].

Since the identification of the virus, the infection continued to spread rapidly, with the first case outside China being reported early in January 2020. On the 11th of March, 2020, Covid-19 was declared a

pandemic by World Health Organization (WHO) [7]. Since then, there have been more than 450 million cases of confirmed Covid-19 infection worldwide [6]. Tremendous efforts resulted in the successful development of several vaccines; however, the continuous emergence of SARS-COV-2 variants keeps threatening the global healthcare stability.

The Infection Pathophysiology

The transmission of the SARS-COV-2 virus occurs via exposure of an individual to respiratory droplets or aerosols, produced from an infected subject through, for example, coughing or sneezing.

The virus then enters the host's cells by binding of the S protein to the Angiotensin 2 Receptor (ACE 2) which are expressed in abundance on the respiratory epithelium (ie type II alveolar epithelial cells) [8].

ACE2 receptors are also expressed by many other organs, including the thyroid gland, pancreas, myocardial cells, and enterocytes and urothelial cells of the bladder. This is the mechanism of extrapulmonary manifestations of SARS-COV-2 induced infection [9].

After the attachment viral replication, endocytosis and assembly of virions is facilitated through priming of the spike protein S2 subunit by the host transmembrane serine protease 2 (TMPRSS2) [10].

SARS-COV-2 induced pneumonia typically occurs in two phases, early and late. The early phase is characterized by direct viral mediated tissue damage, whereas the late is a result of the host's immune system response triggered. The latter is characterized by the release of cytokines such as Interleukin 1 (IL-1) Interleukin 6 (IL-6), Tumor Necrosis Factor – alpha (TNF-a) and Interferon -gamma (INF-γ). Some unfortunate individuals may experience an immune system over-reaction named-"Cytokine Storm" [11]. The release of the cytokines leads to increased vascular permeability, which explains the ARDS (Acute Respiratory Distress Syndrome) that accompanies this phase. Endotheliitis also occurs as a result of direct viral injury to the endothelium, and this predisposes infected patients to thrombotic phenomena frequently observed during this phase. Dysregulation of the Rennin-Angiotensin-Aldosterone system (RAAS) as a result of binding of viral binding to ACE2 Receptors has also been described. This is another possible mechanism explaining the development of interstitial fluid and progression to ARDS [12]. Activation of the Kallikrein -bradykinin system has also been described, which also permits vascular permeability [13].

SARS-COV-2 binding to Toll-Like-Receptor (TLR) releases pro-IL-1β, the precursor of IL-1 β, which eventually leads to lung fibrosis as a result of the ongoing inflammation [14].

Risk Factors for Severe Disease

It has been reported that about 17.9% to 33.3% of the infected patients have no symptoms at all, whereas severe disease was evident in about 23% with a mortality rate of up to 6% as analyzed by a meta-analysis of 212 published articles including 281,461 infected patients from 11 country regions [15, 16].

Although severe disease has been described in young and otherwise healthy individuals, the presence of chronic comorbidities has been strongly associated with severe disease and worse outcome [8]. Also, people aged >60 years, have been more susceptible to complications.

Common medical comorbidities linked to poor outcome are obesity, cardiovascular disease, and diabetes, underlying chronic pulmonary condition, cancer, and organ transplant recipients [8].

Based on a surveillance done by Stokes *et al.*, from January 22 till May 30, 2020, 45.5% of patients with comorbidities needed hospitalization due to Covid-19 infection, as opposed to 7.6% of patients with no previous comorbidities [17].

Prevalence of Covid-19 among Diabetic Patients

Although diabetes itself increases an individual's susceptibility to infections, several sources report a similar incidence of Covid-19 among diabetic patients as compared to the general population [18]. Young *et al.*, concluded in a meta-analysis and systematic review of 8 trials in China, that diabetes was present in 8% of 46248 patients infected with Covid-19, which is quite similar to the average prevalence of diabetes in the general population [19]. Fadini *et al.*, also reported a prevalence of diabetes of 8.9% among hospitalized patients in Padua, Italy [20]. This, again, is similar to the prevalence of diabetes in the general population, thus supporting the theory that diabetic patients are not more susceptible to contract the infection.

Unfortunately, there have been no national surveys published to report with accuracy the incidence of Covid-19 among diabetic patients, and screening for Covid-19 has varied among countries, and, also in different times since the beginning of the pandemic.

However, as previously observed in SARS and MERS in the recent past, so is the case in Covid-19 , as evidence implicates diabetes-particularly poorly controlled diabetes-in moderate to severe Covid-19 infection [21].

Outcome of Diabetic Hospitalized Patients among Variable Centers

Since the beginning of the Covid-19 outbreak, many authors published information reflecting the characteristics of hospitalized Covid-19 infected

patients. They also described the most common comorbidities among moderate-severe infection, and their clinical outcome.

There are several published reports, from different regions in the world, some of which are summarized in the table below:

Reference	Country	Design	Population	Outcome
Zhu *et al.*, [21], 2020	Hubei Province, China	Retrospective, longitudinal, multicenter study (Dec 30,2019- mar 20, 2020)	7337 participants with confirmed Covid-19 infection, aged 18 to 75, including 952 patients with pre-existing diabetes	Diabetes was related to higher need of intensive care, and higher risk of all-cause mortality. Outcome dramatically improved with good in hospital glycemic control for diabetics. (Adjusted HR of ARDS 0.47, (95% CI, 0.05-0.83, p = 0.009) HR of acute heart injury 0.24(95% CI, 0.08-0.71, p= 0.010), HR of acute kidney injury 0.12(95% CI, 0.01-0.96, p = 0.046)) between the well-controlled diabetic group and the poorly controlled one.
Richardson *et al.*, [22], 2020	New York City Area, USA	Case series study of covid-19 infected hospitalized patients , March 1, 2020 April 4, 2020	5700 patients from 12 hospitals were included.	Most common comorbidities were hypertension, 3026 (56.6%) obesity, 1737, 41.7%, and diabetes, 1808, forming 33.8% of the sample. Higher percentage of acute kidney injury among diabetics was observed.
Grasselli *et al.*, [23], 2020	Lombardy region, Italy	Retrospective, observational cohort study, Feb 20 to April 22, 2020.	3988 critically ill patients with confirmed Covid-19 infection referred for ICU admission. Follow up completed by May 30, 2020	Presence of chronic obstructive pulmonary disease (HR 1.68; 95% CI, 1.28-2.19), hypercholesterolemia (HR 1.25, 95% CI, 1.02-1.52), and diabetes (HR 1.18, 95% CI, 1.01-1.39) were strongly related to increased mortality. Also long term use of ACE inhibitors, diuretics, b-blockers and statins were associated with worse outcome.
Casas-Rojo *et al.*, [24], 2020	Málaga, Spain	Multicenter, retrospective cohort study utilizing the SEMI-COVID Registry, March 1, 2020 till June 30 , 2020	15111 patients from 150 hospitals were included, all admitted with confirmed Real Time Polymerase Chain Reaction(RT-PCR) of SARS-COV-2	Hospitalized patients exhibited a high level of comorbidities (61.4%), the most common of which were hypertension (50.9%), dyslipidemia (39.7%), obesity (21.2%) , and diabetes (19.4%).
Pepe *et al.*, [25], 2020	International, information retrieved from the HOPE-COVID-19 Registry (Health Outcome Predictive Evaluation)	Retrospective international study	All patients aged 18 to 64 admitted with confirmed or highly suspected Covid-19 infection registered in the HOPE-Covid-19 Registry (a total of 5868 patients from 39 cities and seven countries, of which 2676 were <65)	Inhospital mortality among the elderly was 32.1%, as compared to 6.8% among the younger cohort, p<0.001. In younger patients (<65), obese individuals had double the mortality rate of non-obese ones, Diabetes was present in 9.1% of the young cohort, and 27% of the elderly. ACEI/ARBs in 19.8%
Barron *et al.*, [26], 2020	United Kingdom	A whole population study	Whole population study elaborating the risk of Covid-19 related in-hospital demise associated with both types of diabetes from March 1 to May 11, 2020.	Prevalence of diabetes is about 5.2% in the general population, whereas it reaches up to 33.6% among Covid-19 deaths. Both type I and 2 diabetes were independently associated with increased mortality rates from Covid-19 after adjusting for confounding factors. Death rates were positively associated with advanced age; this was more pronounced among type 1 diabetic patients rather than type 2.
Bhatraju *et al.*, [27], 2020	United States, Seattle	Prospective cohort, case series	ICU patients with ARDS due to Covid-19 infection, February 24 and March 9, 2020.	Diabetes was the major comorbidity associated with severe infection (58%).

Chen, Liang *et al.*, [28], 2020	China	Retrospective cohort	50 fatal cases out of 1590 included in the study	Diabetes was the second most common associated comorbidity among the fatality group (26%)
Gautret *et al.*, [29], 2020	Marseille, France	Pilot, observational study	a cohort of 80 relatively mildly infected inpatients	Diabetes was present in 11% of the hospitalized patients, only second to hypertension (16%)
Martin-Sánchez *et al.*, [30] 2020	Madrid, Spain	Secondary analysis of Covid-19, retrospective, observational cohort study	1379 laboratory conformed Covid-19 cases admitted to the emergency department	Diabetes was the third most frequent comorbidity (9.2%), preceded by hypertension (40.5%), and dyslipidemia (37.9%)
Schönfeld *et al.*, [31], 2020	Argentina	National database data extraction	207,079 cases included with complete datasets and positive RT-PCR for Covid-19, from March 3 to October 2, 2020.	Diabetes was the second most common comorbidity (9.7%) preceded by hypertension (19.2%) 28% of those who required hospitalization were diabetics. 27% of those who did not survive were diabetics.

Implicated Mechanisms of Worse Outcome among Diabetic Patients Infected with SARS-COV-2 Virus

Increased Risk of Infection in Diabetic Patients

Both types of diabetes have been associated with increased susceptibility to skin, ear, bone, eye, gastrointestinal and respiratory infections, especially when diabetes is poorly controlled. Poorly controlled diabetes also significantly raises the rates of hospitalization and mortality as a result of such infections [32-34] according to Seshasai *et al.,* [35], in a study involving 800,000 participants; the hazard ratio (HR) for a diabetic individual to die from an infection was 2.39. In some trials it has been reported that the risk for type 1 diabetes (T1DM) was even higher than type 2(T2DM) [36]. This applies to viral infections, such as influenza virus and other flu-like infections, as described by Peleg *et al.,* [37] who reports an increased risk of admissions for diabetic patients up to 6 times higher than non-diabetic individuals. Wang *et al.,* [38] describe fasting plasma glucose as an independent risk factor for poor outcome and severe H1N1 infection.

Immunity in Diabetic Patients is compromised

Altered immunity among diabetic patients is multifactorial. In part, this may be attributed to the chronic comorbidities associated with long standing diabetes and the presence of microvascular complications such as nephropathy. Imbalance in gut microbia may explain increased susceptibility of individuals with hyperglycemia to enteral infections [39].

Humoral immunity is generally unaffected by hyperglycemia, however, cellular immunity is greatly changed in diabetic patients, as , for example , impaired chemotaxis, phagocytosis, and altered cytokine secretion in both types of diabetes [40-42]. Studies demonstrate the above alterations are augmented among patients with poor glycemic control, and long duration of diabetes.

There are reports of either increase or decrease in the number of neutrophils in patients with T1DM.

Natural killer cell activity is decreased as well, which is further augmented by obesity, the latter frequently co- exists with T2DM (Insulin Resistance) [43].

T-cell overactivation leading to a chronic state of low grade inflammation has been described in both types of diabetes, with an increased ratio of $CD8^+$ / $CD4^+$, accompanied by augmented release of cytokines. T-cell differentiation is also altered in T2DM, with higher $CD8^+$ percentage compared to $CD39^+$, and increased Th17 cells as well, leading to chronic inflammation [44].

The above mechanisms lead to inappropriate response to viral entry, with an initial delayed release of interferon gamma which is then combined with hyperinflammatory response and may lead to the cytokine storm [45].

However, given the fact that their humoral immunity is unaffected, diabetic patients respond similar to the general population to vaccinations (as, for example, to influenza vaccine) [46].

The Presence of Comorbidities

Diabetic patients are more likely to harbor other medical comorbidities, such as hypertension, renal impairment, and obesity-among others. The presence of these comorbidities is an additive risk factor leading to poor outcome among diabetic patients infected by SARS-COV-2.

Increased Viral Load and Reduced Viral Clearance

SARS-COV-2 enters the cell utilizing ACE2 receptors, which are expressed in several tissues, such as the lungs, pancreas, heart, blood vessels and enteral luminal cells.

Diabetic patients have increased expression of ACE2 receptors, which makes them susceptible to higher viral loads when infected [47].

Viral load may be increased as well by the presence of increased glucose in the airway secretions as a result of hyperglycemia, which has been previously described in influenza infection [48].

A reduction in viral clearance may result from abnormal T-cell response, reduced natural killer cell activity, and impaired complement action [49].

Furin, a type-I membrane bound protease implicated in coronavirus entry into the cell, is generally increased in diabetic patients, resulting in increased viral replication [50]

Plasminogen levels are also increased in diabetic patients, which potentially accentuate the virulence of SARS-COV-2 [51].

Use of Medications

ACEI

Rennin Angiotensin-Aldosterone System (RAAS) inhibitors are commonly used in diabetic patients for their nephroprotective effect. Angiotensin Converting Enzyme Inhibitors (ACEI) inhibits ACE1, which results in upregulation of ACE2 receptors – through which SARS-Cov-2 gains entry into the cells [52]. Furthermore, ACEI use reduces Angiotensin 2 levels and increases Angiotensin 1-7, which reduces cytoplasmic PH, and this on its turn may potentiate viral replication in host cells [53]. Angiotensin 1-7 also binds to the vasoactive Mas receptor in the brainstem, thus potentially increasing the sympathetic activity which may increase cardiovascular events in these patients [54]. Although in theory ACEI use can potentiate Covid-19 infection, several studies demonstrated no increased risk of contracting the virus, and no increased risk of complications and poor outcome once infected [55, 56].

After binding to the ACE2 receptor, SARS-CoV-2 spike proteinase then activated by type II transmembrane serine protease (TMPRS22). These proteases however are of limited number, and this may explain the results of the clinical trials supporting that use of ACEI wasn't associated with increased mortality in diabetic patients with Covid-19 [18]. Also, increased ACE2 and angiotensin 1-7 may have a beneficial effect through increasing vasodilation and reducing fibrosis in animals [57].

Based on the above mentioned data, it has been recommended by the American Heart Association, the European Society of hypertension, and others, to continue treatment with ACEI for patients with Covid-19-unless other contraindications occur [58].

Insulin Sensitizers

Although Metformin should be temporarily or permanently withheld in cases of acute illness, renal impairment or dehydration, some reports describe some benefit in pulmonary tuberculosis and pneumonia [59].

Thiazolidinediones use may result in fluid retention resulting in decompensated heart failure; therefore their use would better be avoided during Covid-19 infection; however they may as well increase ACE2 levels [60].

Incretin-Based Therapy

Glucagon-like peptide-1 (GLP-1) agonists may increase ACE2 levels in diabetic patients as well, and they have been found to increase surfactant in animal trials, however there are only few reports of their safe use among critically ill patients, therefore it is recommended to avoid them during acute illness [61].

Dipeptidyl-peptidase 4 inhibitors (DPP4) have been used in previous viral pandemics, such as MERS (previously described). DPP4 is the entry receptor for MERS coronavirus, and it has been hypothesized that it could be implemented in SARS-CoV-2 entry as well. In the past it had been suggested that their widespread use in India among other countries might actually have some protective effect. However, DPP4 inhibitors may also be potentially harmful as they may alter immunity [62, 63].

Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitors

SGLT-2 inhibitors can cause indirect ACE2 activation, particularly if combined with ACEI. This class can potentially reduce lactate as a result of reduced oxygen requirements at the cellular level. Hence, SGLT-2 inhibitors can theoretically increase cytosolic PH, thus reducing viral entry. However, there is a concern about euglycemic diabetic ketoacidosis and dehydration in acutely ill patients [64].

In general, it is recommended for mildly infected diabetic patients to keep the same pre-infection medications, with the previous precautions mentioned regarding some classes. However, for severe infection and hospitalization/Intensive Care, insulin is the treatment of choice, and maintaining strict glycemic control is crucial to improve the general outcome of those patients [18].

Chronic Endothelial Dysfunction

Patients with diabetes of either type have some degree of chronic low-grade endothelial inflammation which may lead to vasoconstriction and, subsequently, organ ischemia. Hence, diabetes can be considered as a procoagulant condition [65]. It has been also reported that fibrinolysis markers and coagulation factors are upregulated amongst diabetics [66].

This damage can be augmented by the direct effect of SARS-CoV-2 on endothelial cells, leading to the various complications and thrombotic phenomena that may accompany Covid-19, and possibly contributing to the cytokine storm [67].

Diabetic Lung Disease

Several studies indicate diabetic patient's exhibit abnormal pulmonary functions, such as reduced Forced Vital Capacity (FVC), especially in T1DM, reduced Total lung capacity, and impaired alveolar gas exchange [68]. Alveolar lining and endothelial capillary basal lamina through which the exchange takes place are thickened in patients with diabetes [69].

Hyperglycemia leads to increase inflammatory cytokine release, and diabetes is a cause of reduced mucocilliary clearance, which renders diabetic patients more susceptible to lower inspiratory tract infections [70].

All the previously mentioned mechanisms may contribute to having worse outcome among diabetic patients infected with SARS-CoV-2 , however further studies are needed to elaborate into other possible mechanisms, which may serve to target specific therapies aiming to culminate the severity of the disease among diabetic patients and even the general population. Furthermore, SARS-CoV-2 is still evolving and several variants have already caused serial outbreaks, which poses even a further challenge on the healthcare system, with evolving vaccines aiming to target those variants.

CONCLUSION

SARS-CoV-2 virus transmission among diabetic patients is about the same as for the general population. However, it has been reported in several surveys, that diabetic patients are more likely to develop severe disease, and even succumb to Covid-19 infection. In this article I have described the possible mechanisms that may explain these findings.

Better understanding of these risk factors may shed a light on possible mechanisms to reduce disease activity even in non-diabetic patients, and helps to understand thoroughly the virus's behavior.

Tight glycemic control is crucial for diabetics with moderate- severe Covid-19, to avoid the adverse effects of hyperglycemia on the innate immunity.

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