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Diabetes and COVID-19: Mechanism of pneumonia, treatment strategy and vaccine

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ABSTRACT

As of August 5, 2021, there were about 200,000,000 global confirmed patients of COVID-19, with more than 4,250,000 deaths. The COVID-19 disease which is a tremendous public health threat, jumps unpredictably and outbreaks very quickly. The overall mortality rate of COVID-19 infection is 1%–15% but reaches up to 17–38% in older cases with chronic disorders and in intensive care unit (ICU) subjects. Diabetic patients, particularly those whose disease is not well controlled can be more susceptible to COVID-19. Although diabetes was present in 5.3%–42.3% of fatalities from COVID-19, the underlying pathophysiological mechanisms of action of novel coronavirus in diabetic patients are unknown. Based on the elevating of global prevalence, diabetes is the main medical problem associated with COVID-19. It is plausible that diabetes can forecast elevated severity of pneumonia. The mortality of lung infection among diabetes is remarkably higher compared with non-diabetic patients. Mechanisms responsible for severe pneumonia in the diabetic patients as well as treatment of diabetic patients infected with COVID-19 are largely speculative. Hence, this paper will summarize the recent findings related to the mechanisms of pneumonia and treatment strategies in diabetic patients.

1. Introduction

Up to August 5, 2021, about 200,000,000 patients of novel coronavirus (2019-nCoV) have been documented worldwide, including 4,254,127 deaths. Within about two months, the 2019-nCoV spread rapidly throughout China and other parts of the world. Therefore, at present, the number of cases outside of China is very high, and infected cases have been reported in all part of the word [1,2].

The 2019-nCoV is a single-strand enveloped RNA virus (genus β-coronavirus, subgenus Sarbecovirus). Coronaviruses are divided into four genera, including alpha, beta, gamma, and delta coronaviruses. Alpha and beta can infect mammals, while gamma and delta coronaviruses tend to infect birds. The two famous β-coronaviruses, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) cause fatal and severe lung infections. It was identified that the genome sequence of 2019-nCoV is 79.5% and 96.2% identical to the SARS-CoV and bat coronavirus RaTG13, respectively. Based on the 2019-nCoV genome sequencing result, the bats have been reported as common host of virus origin. Hence 2019-nCoV may transmit from bats through unidentified intermediate hosts to humans [3–5].

1.1. COVID-19 infection and pathogenesis

Clinical findings among infected subjects are varied from asymptomatic to mild to a severe or fatal condition. General symptoms of infected cases include shortness of breath (3–31%), fatigue (11–52%), cough (46%–82%), and fever (77–98%) at disease onset [6,7]. It has been reported that some cases had gastrointestinal problems such as nausea and diarrhoea before developing lower respiratory tract signs and fever. One of the main manifestations of 2019-nCoV is pneumonia. Most cases have mild symptoms and good prognosis, while about 20–30% of hospitalized cases require intensive care unit (ICU) for pneumonia [6,8].

Pneumonia is a major common severe manifestation of COVID-19, considered primarily by cough, fever, dyspnoea. Pneumonia may

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progress to lung fibrosis in infected diabetic patients.

The incubation period of 2019-nCoV is approximately 5.2 days, although there is a recommendation that it might be as long as two weeks [9]. According to the recent studies, the latency period is generally from 3 days to one week, with a maximum of two weeks. Of note, this virus is contagious during the latency phase [10].

The main transmission ways are including respiratory droplets, human-to-human transmission, and aerosol transmission. This virus probably is chiefly spread through close contact with patients through the respiratory droplets from sneezing or cough. However, recent studies are also supporting the transmission of COVID-19 by the gastrointestinal tract. For instance, some patients had diarrhoea, and their stools were positive for 2019-nCoV [9].

1.2. Fatality rate and prevalence of COVID-19 in diabetic patients

An overall fatality rate of COVID-19 is about 1–7% among confirmed patients [11,12]. Nevertheless, the majority of these patients were among hospitalized cases, and consequently, this mortality evaluation is probably biased rising. Of note, among hospitalized patients with pneumonia, the fatality rate is approximately 4–15%. Wu et al., evaluated the fatality rate of 72,314 patients in China. The total fatality rate was 2.3% [11]. However, the fatality rate in patients aged over 80 years, patients at age 70–79 years and those in critical conditions were 14.8%, 8.0%, and 49.0%, respectively [11]. The fatality rate is also found different among countries. The fatality rate of COVID-19 in Italy was about 10.8% while in the South Korea it was 1.5% [13]. South Korea has used a complete screening test for SARS-CoV-2. This may have caused the detection of great number of cases with slight or mild symptoms, but resulted in a much lower case-fatality rate in comparison with Italy. Many cases with mild symptom which could not be tested in Italy were included in the screening in Korea. Furthermore, the demographic analysis in Italy differs from other countries. In 2019, about 23% of the Italian population was 65 years old or older. Since the virus is more deadly in older cases, the elderly population rate in Italy may illuminate, in part, the higher patient-fatality rate in Italy compared with that of Korea or other countries [12]. The coexisting conditions might have also elevated the risk of fatality independent of COVID-19 infection [6,14]. Among a subsample of 355 cases of COVID-19 patients that died in Italy, 35.5% had diabetes, 30% had heart disease, 24.5% had atrial fibrillation, 20.3% had active cancer, 9.6% had a history of stroke, and 6.8% had dementia. Generally, less than 1% of reported cases had no diseases while 25.1% had single comorbidity, 25.6% had two comorbidities, and 48.5% had three or more comorbidities [12].

Another report showed 100,23 deaths out of 97,472 confirmed patients until March 29, in Italy [13]. Interestingly, about two-thirds of these cases had diabetes, cancer, and cardiovascular diseases or were elderly. Hyperglycemia and diabetes are usually believed to be risk factors for viral infections and pneumonia [15]. Therefore, due to the susceptibility of diabetic patients to COVID-19 and its high prevalence, diabetes requires more attention. Biochemical findings in patients with COVID-19 in few experiments did not show the relationship between blood glucose and severity of COVID-19 infection [16]. However, a study conducted by Chen et al. showed that 12% of COVID-19 patients (12 out of 99 cases) had abnormal glucose levels [17]. In the same way, by analysing of 72,314 COVID-19 patients, Wu et al. showed elevated mortality (7.3%) in Chinese diabetic patients [11]. In summary, the overall rate of diabetes in COVID-19 varied from 5.3% to 22% [14,18]. As the prevalence of coronavirus disease and infected diabetic patient-related hospitalizations rise worldwide, accurate findings are necessary to detect the mechanism of pneumonia, and to use a proper therapeutic strategy.

2. Prevalence of diabetes

According to the International Diabetes Federation (IDF) report, the worldwide prevalence of prediabetes and diabetes has been significantly increasing over the last decades [19]. The total prevalence of this disorder is estimated to increase from 463 million cases (9.3%) in 2019 to 578 million (10.2%) by 2030 and to 700 million (10.9%) by 2045. The prevalence of diabetes is higher in urban (10.8%) regions than in rural (7.2%) areas [20]. Type 2 diabetes accounts for about 90% of total cases and is related to aging, obesity, and urbanization [20]. Patients often do not know that they have diabetes and approximately 50% of subjects living with diabetes do not discern the presence of disorder. The worldwide prevalence of impaired glucose tolerance (IGT) was 374 million (7.5%) in 2019 and estimated to reach 454 million (8.0%) by 2030 and 548 million (8.6%) by 2045 [20], which among them about 72% live in low-and middle-income countries [20].

3. Diabetes and viral respiratory infections

Lung infections are the main infections related to diabetes [15]. COVID-19 infected patients with underlying diseases (e.g., hypertension, diabetes, obesity, and asthma) are more prone to suffer from complications [6,21]. Lung injury is one of the main cause of mortality in COVID-19 patients [6]. By proper glucose control, the risk of COVID-19 infection could significantly be decreased, although it is not absolutely prevented. In this respect, it has been recommended that all diabetic patients (above two years of age) use pneumococcal and annual influenza vaccinations.

Diabetes is recognized a vital risk factor for mortality in cases infected with SARS coronavirus, MERS coronavirus and influenza A 2009 (H1N1) [6,22]. Diabetic patients are likely to be hospitalized with influenza during this virus epidemic six times more than non-diabetic COVID-19 patients. These subjects are also at increased risk of secondary bacterial pneumonia [23]. Evaluation of about 300 MERS-CoV patients and approximately 93,000H1N1-infected patients showed an overall prevalence of 54.4% and 14.6% for diabetes in MERS-CoV and H1N1 subjects, respectively. This finding may propose an etiological association between diabetes and lung infections [24]. It has been reported that diabetes multiplied the risk of hospitalization after H1N1 virus infection and quadrupled the risk of admission to the ICU [25].

Inokuchi et al. showed that 88% of MERS-CoV patients with diabetes had a poor disease outcome known by ICU admission or death compared with 39% of patients who had any type of non-diabetic coexisting disease. Together these observations suggest that diabetes is the main contributor to the severity of MERS-CoV [26]. Therefore, diabetic subjects are more prone to viral lung infections, and diabetes is accepted as an independent risk factor for pneumonia. Hyperglycemia reduces the clearance virus from the respiratory tract and decreases the phagocytic capacity of WBC [23].

Increased airway glucose levels can raise replication of the respiratory pathogens, proposing that diabetic patients may have elevated bacterial outgrowth after virus infection [25]. Diabetes also is known as a risk factor for other respiratory tract infections, such as *Burkholderia pseudomallei* and *Mycobacterium tuberculosis* [27]. There is a significant positive correlation of the mean serum glucose concentration with respiratory tract infections in diabetic patients. Immunosuppressive, inflammatory and oxidative stress (OS) properties of high glucose levels contribute in viral pneumonia in diabetes. High glucose concentration can decrease degranulation of neutrophil, disturb complement activation, and damage phagocytosis– all of which can elevate the viral infections [25].

In summary, diabetic patients may have high susceptibility to viral pneumonia. Hyperglycemia can increase the risk of lung abnormalities including reduced lung aspiratory function, increased pulmonary microangiopathy, impaired lung structure, reduced immunity, and increased oxidative stress (OS) [25,28,29].

4. Mechanism of pneumonia in diabetic patient infected with COVID-19

Pneumonia is defined as an inflammation and consolidation of the lung because of infection [30]. Due to lung location, anatomy, and function, this organ is more susceptible to oxidative damage [31]. On the other hand, diabetes induces lung oxidative stress and inflammation and increases susceptibility to viral pneumonia. Not surprisingly, COVID-19 infected-diabetic patients have more severe outcome compared with non-diabetes [14,32]. Rueda et al. reported that in non-diabetic cases who had bacterial pneumonia, high blood glucose related with more severity and a worse outcome, particularly when plasma glucose (APG) levels was equal or more than 180 mg/dl at the admission [15]. Therefore, this conclusion can be drawn that monitoring of blood glucose is of immense importance in all COVID-19 infected cases [33].

Diabetes-induced oxidative stress (OS) has a vital role in inflammation and involves in heightened development of pneumonia in the COVID-19 infected cases. Changes in redox signalling and consequently, inflammations are accepted to be part of the main pathogenic mechanism in the prevalence and progression of pneumonia [34]. Oxidative stress is described as an imbalance between antioxidants and oxidants that may affect proteins, lipids, carbohydrates, and DNA [31]. Abnormal OS in the airway alters redox-sensitive mediators and involves in the lung dysfunction [35]. Previous studies established that diabetes induces functional abnormalities in the lung, such as a decrease in volumes, elastic recoil, and diffusion capacity. Hyperglycemia motivates OS by elevating the mitochondrial superoxide anion generation and by increasing the glycosylation of proteins, as well as by activating various signalling pathways which may change pulmonary function and structure. It has been reported that pulmonary vascular resistance increases about 14 days after the onset of diabetes and that abnormal glucose levels motivate OS in lung tissue [30].

Increased mitochondrial OS can also induce alveolar epithelial cell apoptosis. Decreases of epithelial cells cause alveolar membrane damage and fibroblasts recruitment to repair the injury by the accumulation of extracellular matrix. The resistance of fibroblasts to apoptosis may determine persistent matrix deposition with subsequent damage of healthy lung structure [31]. Furthermore, diabetes reduces the humoral and innate immune systems by decreasing the neutrophils and T cells function. Hyperglycemia destroys main components of innate immunity system including phagocytosis, chemotaxis, and the bactericidal properties of macrophages and neutrophils and leads to secondary bacterial infection [24]. Hyperglycemia can elevate the severity and prevalence of bacterial infections. For instance, diabetic subjects with high glycosylated hemoglobin (more than 7%) had a 3-fold elevated risk of active tuberculosis in comparison with those with controlled glycosylated hemoglobin concentration [25]. In patients who had pneumonia, hyperglycemia is associated with a high fatality rate and complications [15]. Moreover, hyperglycemia evokes pathogen growth in the lungs and increases virus replication as well as increasing the risk of secondary bacterial infection [25].

Hyperglycemia can directly raise glucose levels in airway secretions. It has been shown that exposure of pulmonary epithelial cells to increased glucose levels markedly augments influenza virus replication and infection, suggesting that hyperglycemia may act as booster of viral replication [25].

Hyperglycemia reduces lung function by inducing systemic inflammation. Furthermore, hyperglycemia promotes collagen synthesis through induction of OS, increasing of nuclear factor kappa B (NF-κB) gene expression, and enhancing of inflammatory factors, fosters cross-linkage formation through the acceleration of advanced glycation end products (AGEs), and eventually disturbs lung function [36,37].

One of the possible explanations for the higher prevalence of COVID-19 infections in diabetic patients is the defects in immunity [38], since high glucose levels has also been observed in non-diabetic subjects who had acute infections, accompanied with high severity of lung infections. Inflammatory factors, including interleukin-10 (IL-10), IL-1, IL-6, and tumor necrosis factor-α (TNF-α), may contribute to increased glucose concentration by inducing glucose synthesis and elevating insulin resistance. Hence, hyperglycemia in patients who are admitting intensive care units for lung dysfunction, can be the sign of diabetic situation that make them more susceptible to the COVID-19 infection [15,39].

4.1. Treatment of COVID- 19

The human immunodeficiency virus (HIV) protease inhibitors might be useful in the treatment of COVID-19. Currently, a combination of lopinavir/ritonavir (generally used for prevention and treatment of HIV), which was approved for MERS-Cov and SARS-Cov treatment, has been proposed for the management of this novel virus. Nelfinavir is an *anti*-HIV medicine which is postulated to be effective against COVID-19. Remdesivir (a nucleotide analogue), has been shown effective in the treatment of COVID-19 (phase 3 study on the efficacy and safety is ongoing in Wuhan). Chloroquine has anti-inflammatory properties and used for the treatment of malaria. This drug has also been administered for the treatment of COVID-19 [7,8,40].

Umifenovir (Arbidol) has the most widely antiviral properties against influenza disease. This drug can inhibit COVID-19 infection. A phase IV studies of this drug for COVID-19 infection had been registered. Additionally, recent studies have shown that the combination of monoclonal antibody (e.g., CR3022) and remdesivir could probably be effective in the treatment of COVID-19. Furthermore, baricitinib (Janus kinase inhibitor) has been recognized as a potential agent for the treatment of COVID-19 pneumonia through disruption of receptor-mediated endocytosis and interruption of virus entry into the cells [7].

5. Additional treatment strategies for diabetic patients

Currently, there is no specific treatment for COVID-19 in diabetic patients. COVID-19 treatments chiefly focused on symptomatic and pneumonia support based on the experience of SARS-CoV, and MERS-CoV. The 2019-nCoV and SARS-CoV bind to angiotensin-converting enzyme 2 (ACE2) on the epithelial cells of the tongue, lung, kidney, blood vessels, and colon. ACE2 expression significantly increased in diabetic patients, who had treated with ACE inhibitors and angiotensin receptor blockers (ARBs). Ibuprofen and thiazolidinediones also elevated ACE2 expression [8,14]. Scientists do not recommend ibuprofen for the treatment of COVID-19 symptoms [41]. Recent findings show that the treatment of diabetic patients with these medicines can elevate ACE2 expression, and therefore, upregulation of ACE2 could more facilitates COVID-19 infection. In this respect, some scientists supposed that the treatment of hypertension and diabetes with ACE2-motivating medicines could raise the risk of severe and fatal COVID-19 [14]. However, establishment of this assumption may lead to a conflict conclusion since ACE2 decreases inflammatory markers and has been proposed as a possible new target for the treatment of cancer, lung diseases, hypertension, and diabetes [14]. Of note, control of blood pressure is vital in the management of diabetes. At the moment, there is no established scientific relationship between ACE inhibitors and the risk of 2019-nCoV infection.

Infection of diabetic patients with COVID-19 may induce stress situation and alter the release of hyperglycemic hormones (e.g., catecholamines and glucocorticoid), leading to hyperglycemia, and increased diabetes-related complications. Hence, timely glucose monitoring is urgently needed for diabetic cases with COVID-19 [18].

Blood glucose and ketone levels should be controlled in diabetic subjects. A glucose level between 110 and 180 mg/dL and blood ketones level less than 0.6 mmol/L has been recommended [42]. Patients should never stop insulin injections and should drink a high amount of non-sweet fluids (120–180 ml every 30 min) to prevent dehydration [42]. During the one-month follow-up after hospital discharge, glucose

levels should be monitored continuously, and subjects need to be careful about new infectious due to a reduced immune system. However, long time follow-up is still necessary for these patients to decrease diabetes-associated complications [18].

Overproduction and activation of cytokines (cytokine storm) are reported in viral infections which lead to the elevated oxidative stress via a non-specific cascade [43]. Besides current therapy, antioxidant and anti-inflammatory based approaches to quench lung OS and inflammation may alleviate pneumonia, and even promote adverse outcomes in diabetic patients. Early administration of sufficient or high concentration of antioxidants, such as vitamin E, vitamin C and vitamin D as well as natural antioxidants may become a useful treatment of diabetic patients infected with COVID-19. From the available evidences, many health benefits attributed to vitamin D in decreasing the severity, incidence, and risk of pneumonia in COVID-19 subjects are mediated by its antiviral, antimicrobial, anti-inflammatory, and antioxidant properties, which are important in decreasing pneumonia risk [44]. Administration of vitamin C (orally, 6 g daily) significantly reduced viral infection risk or recovered symptoms [43].

Zinc has a vital role in the immune system, and zinc-deficient cases have more susceptibility to infection. Previous studies have shown low zinc status in diabetic patients and older people. Velthuis et al. showed that zinc ions potentially inhibited the replication of SARS-CoV in the cell culture [45]. It has been reported that cases with normal zinc levels had lower pneumonia prevalence, and shorter duration of pneumonia and antibiotic treatment compared to those with insufficient levels [46]. Barnett et al. showed that having insufficient zinc levels may be a risk factor of pneumonia in older people. They recommended that a dose of 30 mg/day zinc may be adequate to increase immune function, and decrease the risk of infections [46]. Zinc nanoparticle also due to potential antioxidant, antiviral, and anti-inflammatory effects, inhibit influenza viral load, and COVID-19 replication in the in vitro experiment [47].

Hyperglycemia may also inhibit the antiviral immune response. The immunosuppressive effects of hyperglycemia can be restored by insulin injection. These observations are in agreement with a study on influenza virus-infected patients, where high glucose levels were related to a fatal outcome [25]. Therefor regular insulin injection in COVID-19 infected diabetic patients probably alleviates pneumonia. Furthermore, receptor for advanced glycation end product (RAGEs) are present in the healthy lung and their expression significantly increased in inflammatory condition, indicating that this receptor has a role in the respiratory inflammation during viral infection. Consequently, inhibition of this receptor during hospitalization in a diabetic patients infected with COVID-19 may prevent severe pneumonia [48].

5.1. COVID-19 vaccine in diabetic patients

People living with diabetes are at higher risk of developing severe symptoms after virus infection, and they are almost 3 times more likely to die due to COVID-19. Hence, diabetic patients are prioritized for early vaccinations since they often experience severe effects than people without diabetes [49]. Various vaccines have been approved for control of COVID-19 infection [50,51]. It has been reported that Johnson & Johnson, Pfizer, Moderna and BioNTech– are effective and safe for people with diabetes. Very rare side effects such as blood clot formation (only around 4 doses of the vaccine in each million doses) was reported in people after the Oxford/AstraZeneca vaccine. However, the benefits of this vaccine outweigh the risks of a blood clot formation in people with diabetes [49,52]. The adverse effects in people following COVID-19 vaccination are generally mild. Furthermore, the diabetic patients can experience mild reactions after COVD-19 vaccines, including mild fever, pain, redness or swelling at the injection site. The severe allergic reactions after COVID-19 vaccine were very rare in people with diabetes [49].

Various vaccines including influenza, hepatitis B, and pneumococcal pneumonia are recommended in diabetic patients. In previous case-control studies, the efficacy and safety of pneumococcal vaccine and pneumococcal polysaccharide vaccine (PPV23) have been shown as ranging from 56% to 81%, and 84% in diabetic patients, respectively. Moreover, optimal B-cell response to seasonal influenza vaccine has been reported in diabetic patients. Patients with diabetes noticeably benefit from influenza vaccination in terms of decrease in any complications, hospitalizations, and mortality [53–55]. One study determined the pneumonia and influenza vaccination in diabetic patient's duration >5.3 years. Very rare side effects, including fever, local rash, aches or pain in joints or muscles were reported in patients [53]. It was reported that about 80% of deaths after COVID-19 infection were among people with comorbidities such as hypertension, obesity, diabetes, and cardiovascular disease. Thus, COVID-19 vaccine is essential for diabetic patients. The Oxford-AstraZeneca vaccine has been recommended in people with comorbidities such as diabetes, cardiovascular disease, obesity, and respiratory disease [53].

It has been reported that control of blood glucose has a potential impact on the efficiency of the immune response [8,9]. Consequently, it seems reasonable that improving blood glucose levels before receiving COVID-19 vaccine may increase immune response [56]. Some recent evidences showed that keeping blood glucose levels in control is desirable for overall well-being, but the COVID-19 vaccine will not interfere with the blood sugar level of people. From 3163 subjects in the Pfizer-BioNTech study, and 2875 people in the Moderna study (phase 3), there was no experiencing of major side effects with the vaccines [49]. The children with diabetes (especially type 1 diabetes) are not at increased risk of COVID-19 infection. However, kids have the potential to transmit COVID-19 to others and should receive vaccines [49]. None of the COVID-19 vaccines have been examined in adolescents less than 16–18 years or children (Pfizer-BioNTech COVID-19 vaccine can be injected for persons aged 16–17 years), therefore, routine vaccination of diabetic patients in this category is not yet recommended. In this respect, many people with type 1 diabetes would be deprived of the same [53].

6. Conclusion

Diabetic patients have high susceptibility to viral infection due to several causes. Mortality among diabetic subjects with COVID-19 is multiple compared with non-diabetic subjects. Specific treatment strategies are needed for diabetic patients who were infected with COVID-19.

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Availability of data and material

Data are available upon reasonable request.

CRediT authorship contribution statement

Ebrahim Abbasi: Project administration, Data curation, Writing, reviewing, and editing. Fatemeh Mirzaei: Methodology, Writing and editing. Heidar Tavilani: Reviewing and editing. Iraj Khodadadi: Project administration, Writing, reviewing, and editing.

Declaration of competing interest

The authors report no conflict of interest.

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