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Prevalence of COVID-19 Among Older People with Type 2 Diabetes Mellitus: A Systematic Review

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ABSTRACT

Background: On March 11, 2020, the WHO proclaimed the Coronavirus Disease 2019 (COVID-19) pandemic owing to coronavirus-2 (SARS-CoV-2). SARS-CoV-2 is a zoonotic virus that may be spread from bats to humans through airborne droplets and aerosols. SARS-CoV-2 spike protein has a high binding affinity for ACE2 receptors, widely expressed throughout the respiratory system, notably in epithelial lung cells. ACE2 receptors are found in intestinal mucosal, endothelial, heart, renal epithelial as well as cerebral neuronal cells, explaining COVID-19 extrapulmonary symptoms like diarrhea, nausea, vomiting, chest pain, heart failure, renal injury, headache, and confusion. Older persons with type2 diabetes mellitus and hypertension are more susceptible to SARS-CoV-2 infection as drugs by which they are treated promote ACE2 receptor expression. Moreover, comorbidities increase the probability of poor outcomes after infection by the SARS-CoV-2. Research links COVID-19 to hyperglycemia in the elderly with type 2 diabetes. Twenty percent of people with diabetes get severe pneumonia and a septic course from viral infections. Diabetes contributed to sickness severity and fatality in MERS (MERS-CoV). Epidemiological findings in SARS-CoV-2-affected regions, CDC data, and other national health centers and hospitals suggest that individuals with diabetes had a 50% greater chance of dying from COVID-19.
Methods: This systematic review involves a critical and reproducible summary of the results of the available publications on COVID-19 and diabetic elderly patients' topics and questions. Fourteen studies (6 retrospective cohorts, two prospective, two cohorts, one combined retrospective, one observational, one cross-sectional, and one hospital-based study) were included in this systematic review.
Results: From all studies, the mean age of older adults with type 2 diabetes mellitus who suffered from COVID-19 was 50 to 89 years. The majority of the studies showed the male predominance of infection. The pooled prevalence of COVID-19 among diabetes mellitus elderly patients was 29.8%.
Conclusions: Diabetes patients had a greater COVID-19 prevalence and severity, according to several explanations. Diabetes Mellitus increases the risk of infection due to innate and adaptive immunity deficiencies. Post COVID-19 complications arise due to a lack of equilibrium between pro-inflammatory and anti-inflammatory cytokine networks in type 2 diabetes mellitus, contributing to increased mortality. Therefore, this study necessitates a large investigational study to find out how to boost the immune response against SARS-CoV-2 infection in an equilibrium manner not to produce much inflammatory cytokine in type 2 diabetes mellitus individuals to reduce the risk of developing complications and mortality consequently.

Keywords: COVID-19, Diabetes mellitus, Type-2 diabetes, Elderly.

CHAPTER 1: INTRODUCTION

1. Background

The World Health Organization (WHO) declared the Coronavirus Disease 2019 (COVID-19) pandemic on March 11, 2020, due to the new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] According to WHO, it was discovered in a market in Wuhan, China, where people traded live and dead wild animals to eat. The whole genome of the virus was sequenced shortly after its discovery and published on January 5, 2020. In barely two months, the virus had spread like wildfire all over the planet. SARS-CoV-2 is a zoonotic virus that may be transferred to humans from animals such as bats and, once adapted, between people through airborne droplets and aerosols. COVID-19 may cause atypical pneumonia with fast respiratory deterioration because SARS- CoV-2 spike protein has a high binding affinity for angiotensin-converting-enzyme 2 (ACE2) receptors, which are extensively expressed in the respiratory tract, especially in epithelial lung cells.[2]

ACE2 receptors have been found in mucosal intestinal cells, endothelial cells of veins and arteries, including heart cells, renal epithelial cells, and cerebral neuronal cells, explaining COVID-19 extrapulmonary symptoms like rhinorrhea, diarrhea, nausea, and vomiting, chest pain and heart failure, renal injury, headache, and confusion. The median incubation period is 5 days, with the majority of people experiencing symptoms by 11.5 days. Clinical deterioration occurs later in the disease, usually in the second week, and is linked with test findings of an immune-mediated cytokine storm generating extensive inflammation and disseminated intravascular coagulation, usually with modest levels of viraemia. COVID-19 risk is increased in frail old people, particularly men, with a history of comorbidities such as diabetes and hypertension treated with ACE inhibitors and angiotensin II Type-I receptor blockers, since these medicines enhance the expression of ACE2 receptors.[3] People with these comorbidities have a much higher risk of poor outcomes.[4] COVID-19 has also been linked to hyperglycemia, especially in the elderly with type 2 diabetes, according to research.[5] Diabetes is a major risk factor for severe pneumonia and a septic course caused by viral infections, and it affects around 20% of patients.[6,7] In the Middle East Respiratory Syndrome, diabetes was discovered as a substantial factor to illness severity and death (MERS- CoV).[8] Evidence from epidemiological observations in SARS-CoV-2-affected areas, as well as reports from the Centers for Disease Control and Prevention (CDC) and other national health centers and hospitals, showed that patients with diabetes have a 50 percent higher risk of dying from COVID-19 than those who do not.[9] There are various theories to explain why patients with diabetes have a higher prevalence and severity of COVID-19 infection. People with diabetes, in general, have a higher risk of infection due to innate immunity defects affecting phagocytosis, neutrophil chemotaxis, and cell-mediated immunity; however, the high prevalence of diabetes in serious cases of COVID-19 may reflect the higher prevalence of type 2 diabetes in older people. Furthermore, diabetes is linked to cardiovascular disease in older people, which might explain the link between COVID-19 and fatal outcomes.

At least two distinct processes are thought to be involved in COVID-19 infection. First, the SARS-CoV-2 virus hijacks an endocrine system involved in blood pressure control, metabolism, and inflammation to gain access to its target cells.[2,3,10] COVID-19 infection causes cellular damage, hyperinflammation, and respiratory failure via lowering ACE2 expression.[10] Acute hyperglycemia has been demonstrated to increase the expression of ACE2 on cells, which may aid viral cell entrance. Chronic hyperglycemia, on the other hand, is known to suppress ACE2 expression, leaving cells exposed to the virus's inflammatory and harmful effects. Additionally, ACE2 expression on pancreatic cells may have a direct impact on cell function.[8-11]

SARS-CoV-2 are single-strand RNA viruses containing four structural proteins: S (spike), E (envelope), M (membrane), and N (nucleoprotein), as well as many ORFs encoding non-structural and auxiliary proteins. There is evidence for additional cell surface molecules such as CD147 and the serine protease TMPRSS29 being coreceptors and/or entry co-factors. SARS-CoV-2 binds to ACE2 with more affinity than SARS-CoV-1, explaining in part the difference in infectiousness. ACE2 catalyzes the hydrolysis of angiotensin II and is a crucial regulator of the renin-angiotensin system; virus-mediated downregulation of ACE2 disrupts the renin–angiotensin system. ACE2 protects against lung, kidney, and cardiac damage. Consequently, at least a portion of disease may be a direct result of viral binding to the host ACE2 receptor. Injection of SARS-CoV-1 spike protein into mice increases acute lung failure in vivo, which is consistent with previous results. ACE2 is expressed in several organs and epithelial cell types in the respiratory airway, with the greatest expression in nasal epithelial cells, indicating that these cells may serve as potential sites of initial infection. SARS-CoV-2 has a direct cytopathic impact on the epithelial cells of the human airways. The effect on endothelial cells led to the development of microvascular complications. The majority of viral shedding occurs in the upper respiratory tract, but fecal shedding also occurs and is often exploited for early epidemiological identification.[83]

The dipeptidyl peptidase-4 (DPP-4) enzyme, which is widely targeted pharmacologically in persons with type 2 diabetes, is a second putative mechanism that might explain the relationship between COVID-19 and diabetes. DPP-4 was discovered to be a functional receptor for human coronavirus-Erasmus Medical Center (hCoV-EMC), the virus that causes MERS, in cell research.[12] DPP-4-specific antibodies stopped hCoV-EMC infection in primary cells. DPP-4 is a type II transmembrane glycoprotein that is widely expressed. It is important for glucose and insulin metabolism, but it also causes inflammation in those with type 2 diabetes. It's unclear if these processes apply to COVID-19 and whether diabetes therapy with DPP-4 inhibitors in clinical practice affects the infection's course, but if they do for SARS-CoV-2, these medicines might lower DPP-4 levels and give therapeutic options for COVID-19.[13]

1.1 Objectives of the StudyGeneral Objectives

To find the prevalence of COVID-19 among the elderly people and patients with diabetes.

1.1.1 Specific Objectives

To assess the prevalence of diabetes among COVID elderly patients

To assess the gender distribution of diabetes elderly people and patients with COVID-19

To assess the mean age of COVID19 in elderly diabetic patients

1.2 Rationale of the study

Diabetes mellitus (DM) is a disease and a global health problem whose severity has worsened over the past two decades.[14] In 1985, 30 million individuals had diabetes; by 2010, that number had risen to 285 million. According to the most recent global projection from the International Diabetes Federation, there will be 463 million diabetic people in 2019. By 2045, it is anticipated that over 700 million individuals would have diabetes.[15,16] Diabetes is the major cause of kidney failure, blindness in adults, and non-traumatic amputations of the lower extremities. In severe cases, complications of diabetes can lead to life-threatening illnesses.[17]

The first pneumonia cases of unknown origin were discovered in China in early December 2019. A new encapsulated RNA beta-coronavirus has been identified as the pathogen.[18] SARS-CoV-2 pneumonia (severe acute respiratory syndrome coronavirus 2) became a well-recognized infection that spread swiftly throughout Wuhan (Hubei province) and other Chinese regions, and continues to spread around the world.[19] The World Health Organization (WHO) has given the SARS-CoV-2-induced sickness the official designation of coronavirus disease 2019. (COVID- 19). By 8 p.m. on April 28th, 2020, the number of patients had climbed dramatically - 2,959,929 individuals had been infected, with 202,733 deaths officially recorded.[20] Patients with COVID- 19 have symptoms such as fever, dry cough, dyspnea, tiredness, and lymphopenia.[21] COVID-19 has indirect impacts on persons who have underlying health problems. For example, while COVID-19 continues to overwhelm many health-care systems throughout the world, a substantial number of non-COVID-19 patients are unable to receive the essential health-care services owing to their pre-existing diseases. Furthermore, many people have been harmed by the reduction in physical activity because by the lockdowns imposed by most countries throughout the world - which is especially important for diabetics. All of these consequences are concerning since they raise the risk of infections, hospitalization, amputations, and potentially death in diabetic patients.[22]

During the COVID-19 pandemic, there are research on diabetes and how to manage diabetic individuals. We want to fill in the gaps in the existing literature by conducting a study that examines current data and determines the prevalence of COVID-19 in elderly diabetic patients, as well as providing preventative and treatment advice for those with both COVID-19 and diabetes.

1.3 LITERATURE REVIEW

1.3.1 Review of Related Literature

One study indicates that the prevalence of diabetes among COVID-19 patients is comparable to that of the general population. There is significant evidence that diabetes increases the risk of serious infections and bad consequences. Diabetes has elevated the development of the condition into acute respiratory distress syndrome, the need for intensive care hospitalization or mechanical ventilation, and the risk of death. Patients with diabetes who are at risk of contracting COVID-19 seem to be obese, older, have uncontrolled glycemia, and associated comorbidities, particularly cardiovascular disease and hypertension. On admission to the hospital, tight glycemic control with insulin infusion has shown some positive benefits; nevertheless, the significance of hypoglycemic drugs in the care of these patients is still unclear.[23] Another study also showed diabetes is a significant independent risk factor, and glucose levels correlate strongly with the course of COVID-19 in older people.[24] People with diabetes had a 79% increased chance of developing severe cases than patients without diabetes, [25,26] thus, it should be regarded a risk factor for the fast development and poor prognosis of COVID-19.[25] Before 2021, a comprehensive evaluation of eight studies including 46 248 Chinese patients revealed that diabetes was the second-most frequent comorbidity (8%), behind hypertension (17 %), among hospitalized COVID-19 patients.[23] Huang et al., 2020, found the prevalence of diabetes 20% among covid-19 patients with a mean age of 49 [27] whereas another study shows 10.2% with a mean age of 57.2.[28] Another study also showed similar prevalence of 10.1%[29] and 111%.[30]

A British analysis of 20,133 hospitalized patients with severe COVID-19 found a median age of 73 years and a prevalence of 21 percent for diabetes.[31] 37.5 % of hospitalized laboratory-confirmed COVID-19 patients were diabetic, according to different research. The average age of all COVID-19 patients was 70,5 years.[32] Holman et al., 2020, showed a mortality rate of type I diabetes (40%) and type II (56.5%) with a mean age of 80.[33] Another study also the prevalence of diabetes among COVID patients was 33.9% with a mean age of 73.[34] Whereas another study showed a prevalence of only 9%.[35] A study conducted in England

(UK) revealed that among 23,804 hospitalized individuals with COVID-19, 32% had type 2 diabetes and 1.5% had type 1 diabetes.[36]

A study in Turkey conducted by Belice et al., 2020 showed the prevalence of diabetes was 32.3%.[37] In another research conducted in Turkey, 157 patients with a median age of 47 were enrolled, of whom 55 % were male and the remainder were female. 14% of 157 individuals were diagnosed with diabetes mellitus (DM).[38]

In USA a study conducted where it showed the prevalent of diabetes was 58% with the average age of the patients was 64, 63% were males,[39] while another survey showed 10.9%.[40] Another study conducted for a short period of time where the prevalence is found to be above 50%.[41] Goyal et al., 2020 conducted study in New York where the result was 25.2%.[42] Compared to those without diabetes, patients with diabetes exhibited a considerably more severe form of COVID-19 and higher death rates. In addition, inadequate glycemic management is related with a considerably greater incidence of severe COVID-19 and increased mortality compared to those with optimal glycemic control.[43] Depending on the series, diabetes is one of the most prevalent comorbidities in COVID-19 patients, with a prevalence ranging from 7 to 30 percent.[44] Kumar et al., 2020, also report that diabetes was linked with severe COVID-19 with a pooled hazard ratio of 2.75 (95% confidence interval: 2.09–3.62; p 0.01). The overall prevalence of diabetes among COVID-19 patients was 9.8 percent.[45]

As of March 19, 2020, Italy was the second nation most impacted by SARS-Cov-2 (n = 41,035 persons with confirmed SARS-Cov-2), and 8.9 percent of its population had diabetes.[46] In a retrospective study done by Grasselli et al., 2020, on 1591 COVID-19 patients hospitalized between February 20 and March 18, 2020, the median (IQR) age was 63 (56-70) years, 1304 (82 percent) were male, and the prevalence of diabetes was 17.0 percent.[47] Another study showed the prevalence from 30-36%.[48,49]

A retrospective observation study conducted by Gupta, 2020, in India and initially the prevalent of Diabetes among COVID elderly patients was low, 3%.[50] 40% of the cohort had a weight increase tendency, with 16 percent of the population reporting a 2.1–5 kg weight gain during COVID-19. When all risk indicators were assessed using the ADA risk engine, the ADA diabetes risk score increased in 7% of the population, with 6.66 percent falling into the high-risk category.[51] India, the diabetes capital of the world, has recorded 236,657 instances of COVID-19 with 6642[52] fatalities and among them a prevalence of 24% diabetic patients with an average age of 61.5 was found.[53]

As of September 24, 2020, the number of SARS-CoV-2 infections in Bangladesh has risen to roughly 352,288 while the death toll stands at 5,040. Among other common illnesses and disorders in Bangladesh, diabetes rates are increasing at an alarming pace, and the International Diabetes Federation (IDF) reports that there are 8.4 million cases of diabetes among adults in Bangladesh.[54] In one research, 734 instances were recorded, of whom 80.11 % did not have diabetes and 19.89 % did; one-third of the COVID-19 patients with diabetes belonged to the older age group (60 years).[55] A retro-prospective examination of 405 patients admitted to the Mugda Medical College and Hospital in Dhaka, Bangladesh was done. The mean age of 405 patients was 46.33 years. Approximately 216 (53.3%) of the patients were male. Among the 405 patients, the prevalence of diabetes was 34.6%.[56]

CHAPTER 2: METHODS

2.1 Study design

This systematic review involves a critical and reproducible summary of the results of the available publications on COVID-19 and diabetic elderly patient's topic and questions. To improve scientific writing, the methodology is shown in a structured manner to implement a systematic review.

This study followed systematic literature review method. The systematic review followed the following criteria:

Acquisition of evidence

The review process was well developed and planned to reduce biases and eliminate irrelevant and low-quality studies. The steps for implementing a systematic review include:

correctly formulating the COVID-19 diabetic elderly patients question to answer

developing a protocol based on inclusion and exclusion criteria

performing a detailed and broad literature search and screening the abstracts of the studies identified in the search and subsequently of the selected complete texts (PRISMA).

Synthesis of the evidence

Necessary data was extracted into a form designed in the protocol to summaries. The biases of each study were assessed. The quality of the available evidence was identified. Tables and texts that synthesize the evidence was developed.

2.1.3 Source of Data

The secondary sources of data included different published topics from national and international journals.

2.1.4 Sample and sampling

Good number of Journal articles was taken regarding COVID-19 and diabetes in recentyears.

2.1.5 Data collection, Data processing and Analysis

Published articles were collected from Renowned indexing data source like PubMed, Medline, Scopus indexed articles. Systematic literature review followed by PRISMA model.

2.1.6 Ethical Issues

Study was performed from different topics regarding diabetic comorbidities during COVID-19 pandemic published in different journals from national and international as research was a systemic review. It was ensured that the data and facts and recommendations was used properly without any alteration. Regarding recommendations proper attention must be given for socio-cultural moms. Data source was properly acknowledged and cited properly.

2.1.7 Data Analysis

After collecting data in some cases, it was analyzed as per systematic literature review and based on results the discussion was prepared.

2.1.8 Limitations

It's a review study and quality article and literature are rare in this topic therefore may be some bias in this study. Meta-Analysis is not included in this study but some study findings included through graph and figures. As it is a review study primary data were missing in this study.

CHAPTER 3: RESULTS

3.1 Distribution of age in COVID-19 older people with type 2 diabetes mellitus

In a Cohort study by Mc Gurnaghan et al, in 2021 a total no of 5463300 population studied where most of the patients were 60 years old and in another cross-sectional study by Zimin et al in 2022 found the same age range 50-59 years old followed by Agarwal et al in 2021 in his retrospective cohort study found the highest patients' rates of patients age was 67.9 years. (Table 1) The following table shows the details:

3.2 Distribution of sex in COVID-19 older people with type 2 diabetes mellitus

In a Cohort study by Mc Gurnaghan et al, in 2021 a total no of 5463300 population studied where 47.3% female and 52.7% male and in an another cross sectional study by Ziminetel in 2022 found 56.3% female and 43.7% male followed by Agarwal et al in 2021 in his retrospective cohort study found that 50.9% female and 49.1% male. (Table 2) The following table shows the details:

Table-1: Age distribution of COVID-19 Elderly people with Diabetes

Author	Country of origin	Population(s) studied	Methodology	Results
Zhang et al., 2021[24]	China	142	Retrospective cohort study	median age was 67 (IQR, 62–72)
Xiong et al.,2021[58]	China	538	Cohort study	the median (interquartile range) age was 52.0 (41.0–62.0) years
McGurnaghan et al., 2021[59]	UK, Scotland	5 463 300	Cohort study	60 years
Izzi-Engbeaya et al., 2021[60]	UK	889	Retrospective cohort study	average (±SD) age was 65.8 (±17.5)
Sourij et al.,2021[61]	Austria	238	combined prospectiveand retrospective	71.1 ± 12.9 years
Infante et al., 2021[62]	Italy	137	Retrospective study	89 years
Seiglie et al., 2021[63]	USA	178	Retrospective cohort study	66.7 years
Agarwal et al.,2021[64]	USA	1276	Retrospectivecohort study	67.9 years
Mithal et al.,2021[65]	India	401	Prospective, observational, cross-sectional study	54 years
Mittal et al., 2021[66]	India	108	Prospective study	55.2 years
Raghavan et al., 2021[67]	India	845	Observational study	60 ± 13
Sharif et al.,2021[68]	Bangladesh	799	Retrospective cohort study	60-69
Saha et al.,2021	Bangladesh	168	Hospital based study	69

Table-2: Gender distribution of COVID-19 Elderly people with Diabetes

Author	Country of Origin	Population(s) Studied	Methodology	Results
Zhang et al., 2021[24]	China	142	Retrospective cohort study	45.8% female and 54.2% male
Xiong et al., 2021[58]	China	538	Retrospective Cohort study	54.5% female and 56.5% male
McGurnaghan et al., 2021[59]	UK, Scotland	5 463 300	Cohort study	47.3% female and 52.7% male
Izzi-Engbeaya et al., 2021[60]	UK	889	Retrospective cohort study	40% female and 60% male
Sourij et al.,2021[61]	Austria	238	Combined prospectiveand retrospective	36.4% female and 63.6%male
Infante et al., 2021[62]	Italy	137	Retrospective study	35% female and 65% male
Seiglie et al., 2021[63]	USA	178	Retrospective cohort study	38.2% female and 61.8% male
Agarwal et al.,2021[64]	USA	1276	Retrospective cohort study	50.9% female and 49.1% male
Mithal et al.,2021[65]	India	401	Prospective, observational,cross-sectionalstudy	31.2% female and 68.8%male
Mittal et al., 2021[66]	India	108	Prospective study	48.78% female and 47.76%
Raghavan et al., 2021[67]	India	845	Observational study	34.6% female and 65.4% male
Sharif et al.,2021[68]	Bangladesh	799	Retrospective cohort study	34.2% female and 65.8% male
Saha et al.,2021	Bangladesh	168	Hospital based study	20.2% female and 79.8% male

3.3 Prevalence of COVID-19 older people with type 2 diabetes mellitus

In a Cohort study by Mc Gurnaghan et al, in 2021 a total no of 5463300 population studied where 5.8% patients had diabetics and in an another cross sectional study by Zimin et al in 2022 found 5.5% patients had diabetics followed by Agarwal et al in 2021 in his retrospective cohort study found that 7.5% patients had diabetics. (Table 2) The following table shows the details:

Table-3: Prevalence of COVID-19 Elderly people with Diabetes

Author	Country of Origin	Population(s) Studied	Methodology	Results
Zhang et al., 2021[24]	China	142	Retrospective cohort study	38.2%
Xiong et al., 2021[57]	China	538	Retrospective Cohort study	7.4%
McGurnaghan et al., 2021[58]	UK, Scotland	5 463 300	Cohort study	5.8%
Izzi-Engbeaya et al., 2021[59]	UK	889	Retrospective cohort study	38%
Sourij et al.,2021[60]	Austria	238	Combined prospectiveand retrospective	80.2%
Infante et al., 2021[61]	Italy	137	Retrospective study	10%
Seiglie et al., 2021[62]	USA	178	Retrospective cohort study	8.1%
Agarwal et el., 2021[63]	USA	1276	Retrospective cohort study	7.5%
Mithal et al.,2021[64]	India	401	Prospective, observational,cross-sectionalstudy	47.1%
Mittal et al., 2021[65]	India	108	Prospective study	8.08%
Raghavan et el., 2021[66]	India	845	Observational study	50.1%
Sharif et al., 2021[67]	Bangladesh	799	Retrospective cohort study	59%
Saha et al., 2021	Bangladesh	168	Hospital based study	52.3%

CHAPTER 4: DISCUSSION

In our review, we included a total of 14 studies (6 retrospective cohort studies, 2 prospective studies, 2 cohort studies, 1 combined retrospective studies, 1 observational study,1 cross-sectional study and 1 hospital-based study design). With a total of 14 studies, 5479564 patients were finally included. The pooled prevalence of diabetes mellitus among COVID elderly patients were 29.8% (n=1589073) found in our studies. Diabetes is one of the commonest occurring lifestyle disorders globally, which is related with multi-system damage in the long term. It is one of the arms of the complicated branch of metabolic syndrome X, which brings with itself several other chronic illnesses. The vulnerability to COVID-19 infection rises in people with diabetes as their immune systems is greatly lowered. Literature suggests a diabetes prevalence of 7.87 percent to 20 percent in COVID-19 patients.[77-80] Another study also showed the prevalent was 16.8% and there is an increased risk of mortality rate.[81]

As it is already known, the COVID-19 infection is more severe in older persons, but it affects all age groups. In our study the most prevalent average age was 64.09±9.57. Extreme pro-inflammatory cytokine production, often known as cytokine storm, seems to be a crucial pathophysiological mechanism in older COVID-19 patients.[69] Numerous studies have shown that elderly individuals have higher levels of interleukin (IL)-6, IL-1, tumor necrosis factor- (TNF), and C-reactive protein (CRP). Despite this, the precise underlying mechanism of cytokine storm in older persons with severe COVID-19 infection is not entirely understood. Nonetheless, it is probable that disruption of cytokine homeostasis in the "inflame-aging" phenomenon plays a crucial role in the likelihood of a cytokine storm and, consequently, acute respiratory distress syndrome (ARDS) in some elderly individuals with severe COVID-19 infection.[70] It appears that the "cytokine storm" phenomenon in elderly patients with severe COVID-19 infection is associated with numerous age-related pathophysiologic processes, such as altered angiotensin-converting enzyme 2 (ACE2) receptor expression, excess ROS production, alteration of autophagy, the inflammatory phenotype of senescent cell activity, particularly adipose tissue, and immune-senescence, as well as a deficiency of vitamin D.[71-76] (Figure 1).

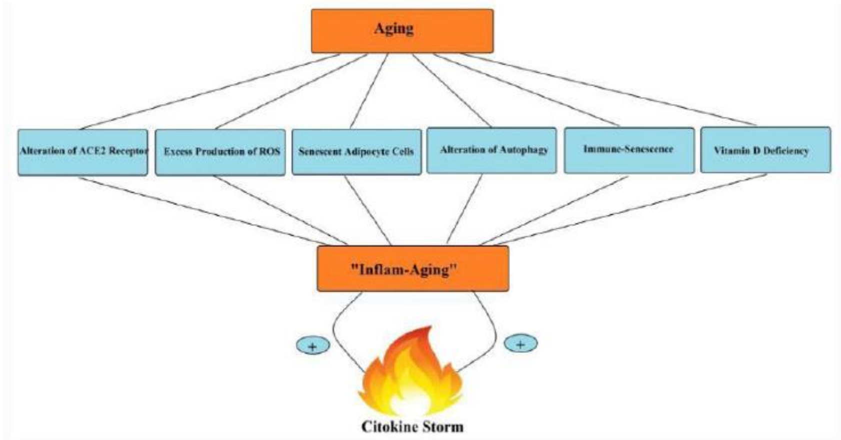

Figure 1: **The link between "inflame-aging" and cytokine storm in in elderly adults with severe COVID-19. Several aging-related factorsmay associate chronic inflammation to cytokine storm in elderly patients of COVID-19**
Adapted from: The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflame-aging" https://link.springer.com/article/10.1007/s00011-020-01372-8

Reduced phagocytic ability and impaired/delayed migration, differentiation, and cytokine generation by innate immune cells are often responsible for age-related deficiencies in innate immunity. In elderly people, cytokine signaling and effector molecule synthesis are diminished in neutrophils. Defects in pattern recognition receptor (PRR) expression and signaling have been found to contribute to the impaired pathogen-response of aged neutrophils. These alterations have been associated with a poor outcome in bacterial infections, such as sepsis.[83,84] Old macrophages also demonstrate diminished migration and phagocytosis, which, interestingly, results in diminished clearance of dying inflammatory neutrophils in the lungs of aged mice after influenza infection, indicating that comparable pathways may contribute to severe COVID-19 pathology.[85,86]

Diabetes and COVID-19 have a convoluted and bidirectional connection. Diabetes is one of the most significant risk factors for severe COVID-19 infection. In a diabetic patient, the concomitant comorbidities and diabetes-related problems, as well as specific demographic characteristics, might contribute to this increased risk of a severe COVID-19 course. Glucose management is an additional crucial aspect. On the one hand, hyperglycemia is a significant risk factor for a COVID-19 course that is more severe. On the other hand, the hyperinflammation associated with severe COVID-19 and its treatment with corticosteroids can cause or worsen hyperglycemia through an effect on insulin target tissues (primarily liver, muscle, and fat cells) that reduces insulin sensitivity (insulin resistance), as well as on pancreatic -cells that leads to inadequate insulin secretion. There may be a direct impact of SARS-CoV-2 on -cells through the ACE-2 receptor, however this is debatable. Hyperglycemia may result in glucose toxicity, reducing insulin sensitivity and insulin secretory function further. Thus, the probability of severe COVID-19 infection is raised further for diabetic individuals (Figure 2).

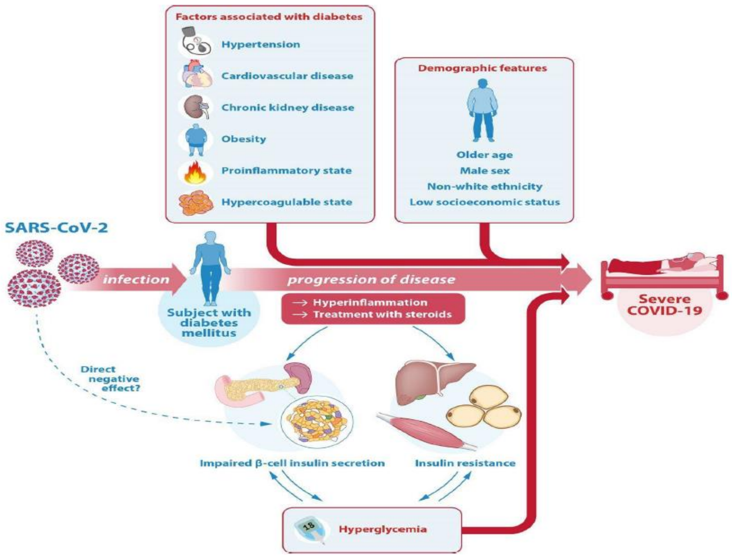

Figure 2: Illustration of the interrelationship between SARS-CoV-2, COVID-19 and diabetes.
Adapted from: COVID-19 and Diabetes: Understanding the Interrelationship and Risks for a Severe Course
https://www.frontiersin.org/articles/10.3389/fendo.2021.649525/full

Although diabetes and age appear to be an independent risk factor for severe COVID-19, the most important factors that co-contribute to an increased risk of COVID-19 severity and
mortality in patients with diabetes are advanced, hypertension, cardiovascular disease, chronic kidney disease, obesity, a proinflammatory and hypercoagulable state, and glucose dysregulation. All of these characteristics must be considered when calculating the probability of a more severe COVID-19 course in diabetic individuals.
It is essential to note that some of these risk factors may be altered. For instance, greater glucose control (i.e., better diabetic (self-)management) and a healthy BMI instantly reduce the probability of COVID-19 infection with a severe course. It is essential for health care workers in the field as well as diabetic patients to be aware of the role they play in minimizing their risk of COVID-19 severity to the greatest extent feasible.

CHAPTER 5: CONCLUSIONS

As the epidemic continues, more information becomes available, but there are still obstacles to understanding the relationship between diabetes and COVID-19. Particularly, more study is required to determine the therapeutic significance of the possible direct influence of the virus on the function of pancreatic -cells through the ACE-2 receptor, as established in in vitro and ex vivo experiments. Young adults seem to have an equilibrium between pro-inflammatory and anti-inflammatory cytokine networks. Therefore, their immune system can restrict the development of COVID-19 infection due to its equilibrium. However, aged people lack the same immunological balance as younger ones. As illustrated in Figure 5, the immune system tends to maintain a state of moderate inflammation with increasing age. Thus, stimulation of the body by pathogens, such as COVID-19 infection, may amplify the immune response to an excessive degree, a phenomenon known as a cytokine storm. As stated before, alterations in ACE2 receptor expression, oxidative stress, adipose tissue- and immune-senescent cell activity, lack of VD content, and decreases in autophagy and mitophagy may all contribute to the high amplitude of the immunological response in aged persons. This increased amplitude of the immune response in older individuals might facilitate the production of the cytokine storm and mortality in instances of COVID-19 infection that are severe and life-threatening. However, COVID-19 infection is not fatal in all old people due to the fact that the aging process is based on several variables, such as genes, lifestyles, and individual variation in immune responses to pathogens.

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