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Impact of COVID-19 in Diabetes, Asthma, and Cardiovascular Diseases

Sana Javaid Awan, Javeria Hafeez, Tayyaba Ajmal, Shafaq Hafeez, Fajjar Azhar, Sehar Munir, Faria Zainab, Nadia Khan, Shamalia Inayat*

1. Zoology Department, Kinnaird College for Women, Lahore, Pakistan.

***Corresponding Author's Email ID:** sana.javaid@kinnaird.edu.pk

ABSTRACT: *SARS-CoV-2 a RNA virus, is a novel virus that belongs to the Coronaviridae family and has caused the most lethal pandemic of the current century. Various variants of SARS-CoV-2 have been circulating since the start of the COVID-19 outbreak. Its variants are Alpha, Beta, Gamma, Delt, Mu and Omicron. The fusion of the viral envelope and host membrane occurs when the spike protein of the virus interacts with the host's ACE2 receptor, resulting in the release of viral RNA into the cytoplasm of the host cell. This process is a crucial step in the viral replication cycle, as it allows the virus to hijack the host cell's machinery to produce more copies of itself. Post-COVID-19 complications such as reduced blood flow to the pancreas, myocardial damage and elevated blood clotting levels have been observed. Studies have shown that individuals with obesity, diabetes, and hypertension are more susceptible to contracting COVID-19. There is still an ongoing debate among experts regarding the impact of asthma as a premorbid condition on the course of the disease caused by SARS-CoV-2. The goal of this review is to give a general description of SARS-CoV-2 and highlight COVID-19's potentially negative effects on health.*

Keywords: *SARS-CoV-2, COVID-19, Variants of SARS-Cov-2, POST COVID-19 Complications*

INTRODUCTION

An increasing number of individuals are recovering from the disease but still dealing with its after effects after their initial infection has subsided as the COVID-19 pandemic continues to grip the world (Carlsten et al., 2021). These lingering symptoms, sometimes known as "long COVID" or "post-COVID syndrome," can last for weeks

or even months and have a major impact on the affected person's quality of life. Little is known about the wide spectrum of post-COVID-19 health manifestations that might affect different organs and systems in the body, despite the fact that the respiratory symptoms of COVID-19 are well-documented (Vu and McGill, 2021). Many of the most often reported post-COVID-19 health symptoms are briefly reviewed in this article, along with their possible causes while the data was gathered from several articles. In order to create efficient post-COVID-19 care methods and enhance the outcomes for persons impacted by this novel disease, healthcare practitioners and policy makers must have a thorough understanding of these symptoms.

SARS-CoV-2 Genotype

A new type of coronavirus known as SARS-CoV-2 caused a sudden outbreak of viral pneumonia in Wuhan, China, which then quickly spread to become a pandemic (Yasmeen et al., 2021; Yasmeen and Chaudhry, 2022). Based upon the phylogenetic relationships of genotypic structure, COVID-19 belongs to the genera "Betacoronavirus". In humans, Betacoronaviruses (SARS-CoV-2, SARS-CoV, and MERS-CoV) have various similarities. Still, their genomic and phenotypic structures already have some different features that may affect their pathogenesis. It is a single-stranded RNA (ssRNA) negative sense particle (Chen et al., 2020).

Variants of SARS-CoV-2

All types of viruses, including SARS-CoV-2, COVID-19 progress over time and change their properties. The term "variant" is utilized to refer to a subtype of a virus that possesses genetic differences from the main strain, but these differences are not significant enough to categorize it as a separate strain. Depending on the changes in the virus's genetic material, mutations may affect coronavirus properties such as transmission or strength (Chen et al., 2020).

Various variants of corona SARS-Cov-2 that are Alpha (the earliest recorded samples in Sep-2020), Beta (the

earliest recorded samples in May-2020), Gamma (the earliest recorded samples in Nov-2020), Delta (the earliest recorded samples in Oct-2020), Mu (Being Monitored:Sep-2021), R.1 Omicron (the earliest recorded samples in Nov-2021) and shown in (Fig. 1).

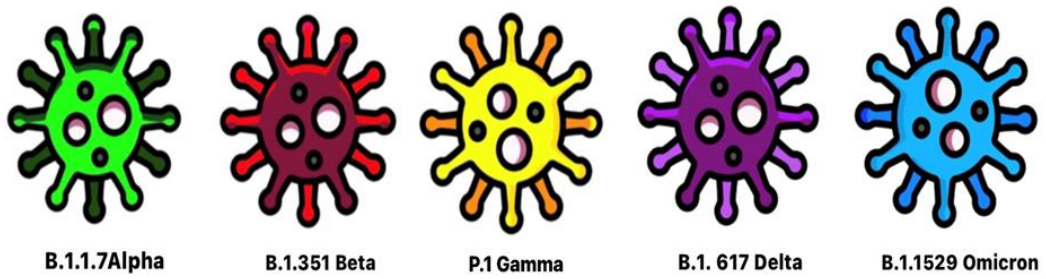

Fig. 1. Various variants SARS-CoV-2 (adopted by Chrysostomou et al., 2023)

Lifecycle and genomic structure of SARS-CoV-2

SARS-CoV-2 is a spherical, enveloped virus that has single-stranded negative sense RNA. SARS-CoV-2 consists of four structural proteins i.e., Spike protein, membrane protein, envelope protein, and nucleocapsid protein. The spike protein binds to the host cell to begin the early stage of the virus life cycle. The initial phase of the virus life cycle begins with entrance of virus into the host cell after the spike protein binds to the ACE2 receptor on the host cell (. SARS-CoV-2 entrance occurs either by endocytosis or through direct fusion. The action of cathepsin L in lysosomes seems to stimulate further processing, which eventually promotes the fusion of the viral envelope with the host membrane and the release of the viral RNA (De Haan et al., 1998). Then the Virus hijacks the biosynthetic machinery of the host cell and starts viral replication. Viral copies are released with bursting of the host cell and cause severe respiratory infection in the host's body.

POST COVID-19 Implications

1. Diabetes Mellitus

COVID-19 is a global pandemic that continues to pose unprecedented challenges worldwide. It is caused by enveloped RNA beta-coronavirus

(SARS-CoV-2) (Viswanathan et al., 2021). Pakistan, Indonesia, Mexico, India, the United States of America, Brazil, and Bangladesh are the top seven countries with the highest prevalence of diabetes. They are the top 8% contributors to coronavirus deaths worldwide.

This may significantly impact COVID-19-related mortality (Viswanathan et al., 2021). It was also observed that some patients having no previous history of diabetes developed Diabetic ketoacidosis (DKA) when exposed to SARS-CoV-2(Bhutani and Bhutani, 2014; Blind et al., 2018).

SARS-CoV-2 acts on the ACE2 receptors and gets entry into the pancreatic cells. By using ACE2 immunostaining of pancreas tissue, an interesting study conducted by Thaweerat et al. (Thaweerat, 2020) revealed that the endocrine part of the pancreas surprisingly has more ACE2 receptors as compared to its exocrine one (Thaweerat, 2020). The endocrine region of the pancreas control the blood glucose levels (Roder et al., 2016). SARS-CoV-2 invades the pancreas and the immune system, and destroys pancreatic cells lowering insulin production, thus resulting in DM, which is the most common in severe cases of COVID-19 (Kamrath et al., 2020; Liu et al., 2020; Marchand et al., 2020; Oriot & Hermans, 2022). This process is activated because of SARS-CoV2 infections, leading to the formation of antibodies in pancreatic cells (Op de Beeck and Eizirik, 2016).

The hypothesis linking DM-COVID-19 suggests that the coronavirus may harm the islet cells in the pancreas, leading to impaired insulin levels and potentially causing diabetes (Liu et al., 2020; Thaweerat, 2020).

This pathway is also mentioned in ifferent studies (Baracchini et al., 2020; Mota and Stefan, 2020) in their work on COVID-19.

In addition, endocytosis of COVID-19 lowers the level of ACE2, leading to increased levels of Angiotensin II. Angiotensin II is a potent vasoconstrictor which inhibits action of nitric oxide in the endothelium of the islet capillaries (Balasubramanyam, 2020), and decreased the blood supply

to the pancreas. Islet cells comprised 15 percent blood supply to the pancreas and now makeup only 1 to 2 percent of the pancreatic volume (Jansson and Hellerström, 1983). The decrease in blood flow to islet cells caused by vasoconstriction hinders insulin secretion in the pancreas. This confirms the bidirectional relationship between COVID-19 and diabetes (Carlsson et al., 1998). Barron et al. claimed that the entire population of England has both type 1 and type 2 diabetes. According to a survey conducted in the USA, people with diabetes mellitus are more likely to experience other consequences of COVID-19 (Zhang et al., 2013). Diabetes related SARS-CoV-2 pathway is also shown in Fig. 2

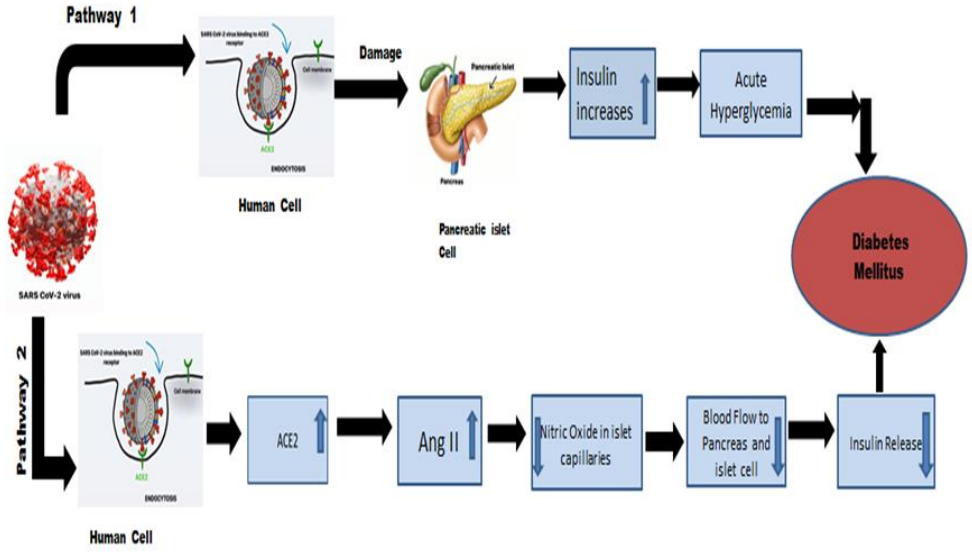

Fig. 2. Diabetes related SARS-CoV-2 pathway (adopted by www.fda.gov)

2. Cardiovascular Diseases

The emergence of the SARS-CoV-2 has presented an unequal challenge to the global health community. The rapid spread of the coronavirus and the resulting epidemics were facilitated by the potential for infection during the asymptomatic phase. Heart disease and various other factors (age, male sex, current smoking, hypertension, and diabetes) increased incidence of coronavirus (Wu and McGoogan, 2020). According to research, SARS-CoV-2 can worsen underlying

cardiovascular disease and cause acute heart problems. Although SARS-CoV-2 main target is the respiratory tract, it may also affect the cardiovascular system. The following are typical routes by which SARS-CoV-2 patients experience cardiovascular issues (Li et al., 2020; Xiong et al., 2020).

1. SARS-CoV-2 causes direct myocardial injury. The virus enters human cells through ACE2. They are abundant within the heart and pancreas. ACE2 regulates the neurohumoral role of the cardiovascular system in both normal and disease conditions. SARS-CoV-2 is attached to ACE2 and can alter the signalling pathways of ACE2, which may cause an acute myocardial injury (Li et al., 2020; Xiong et al., 2020; Yasmeen et al., 2021).
2. Severe cases of SARS-CoV-2 are usually characterized by systemic inflammation (SI) that combined with less oxygen can cause an acute respiratory illness that impairs myocardial oxygen demand and supply relations, leading to myocardial injury.
3. The usage of antiviral drugs, corticosteroids, and other medicines for treating COVID-19 may negatively affect the cardiovascular system.
4. An increase in coronary blood flow causes inflammation, resulting in rupture of coronary artery thrombosis, and causing acute myocardial infarction. Systemic inflammation causes a prothrombotic milieu that further increases the cardiovascular disease risk.
5. Acute myocardial injury (AMI) is the most common cardiovascular complication observed in viral infections. AMI is the death of cardiomyocytes manifested by an increased level of cardiac troponin I (cTnI). Although various cases are related to acute cardiac injury, approximately 7-11% of the positive cases have high cTnI levels (Lippi & Plebani, 2020). The meta-analysis of the Chinese research (B. Li et al., 2020)

claimed 8% of cases of acute cardiac injury; on the other hand, other studies include only patients who had definite outcomes meaning either death or discharge. Discharge from hospitals have shown 16.5% incidence of cTnI level (Zhou et al., 2020). Consistently, AMI has acted as a negative powerful prognostic marker in COVID-19 patients regardless of the actual cases (Huang et al., 2020; Wang et al., 2020; Zhou et al., 2020). Patients admitted to the ICU due to serious illness have a systematic risk of high troponin levels. In contrast, high troponin incidence was significantly lower in patients with minor illnesses that did not require ICU admission. In Pakistan, one in every seven children who develop moderate to severe COVID-19 dies, and the mortality rate is substantially higher than in Western nations.

3. Thrombosis

COVID-19 has affected more than 1/3rd of patients worldwide, as a result of affliction with high blood clotting levels. Even the first ninety nine covid patients admitted to hospitals in China show high D-dimer levels in the blood. Autopsies of people who died due to COVID-19 had shown widespread clots. Disseminated intravascular coagulation and thrombosis are two very common problems in SARS-CoV-2 infection. The blood clot has consumptive nature that lowers the concentration in the circulation of blood. Deletion of the clotting factors accounts for continued bleeding. Clotting results in rupturing of vessels and hemorrhagic stroke. In exuberant clotting, an anticoagulant protein, PROS1 acts with an active protein C to degrade Va and VIIIa factors, terminating the clots. In the coagulation cascade, it is an important inhibitory gene. The absence of PROS1 within mice are lethal, resulting in catastrophic blood clotting (CBC) and hemorrhage. Development

of immune hyper-reaction worsens COVID-19 patients' health. PROS1 is an anticoagulant in the blood coagulation cascade series. The high levels of TNF, IL-1, IL-6, and Interferon-γ concentration dramatically damage multiple sites pleiotropically. The researcher believed that PROS1 has a link with immune hyper-reaction and blood clotting. PROS1 is also the activating ligand of the TAM (Tyro3, Axl, and Mer) family of Tyrosine kinases receptors (RTKs) (Lemke, 2013). RTKs show macrophages, dendritic cells, and other immune bodies in the immune system. MER (Membrane estrogen receptor) is a kinase. When both TAM activating ligands, PROS1 and Gas6, bind to the extracellular domain of MER, MER signaling is activated that reduces type 1 interferons such as TNF and production of other cytokines (Lemke, 2013; Rothlin et al., 2007). A decrease in TAM receptor signals also decrease PROS1 expression.

4. Asthma

Asthma has become a serious health challenge for people 18-50 years old (Network, 2014). Every year more than 12 million people get affected by asthma in the United States (Fergeson et al., 2017). It is an infectious disease caused by COVID-19. The severity of coronavirus can range from mild to severe (Li et al., 2020). The effects of COVID-19 on asthma patients are less proven (Johnston, 2020). Conversely, the impact of coronavirus is closely linked to age.

In Castilla La-Mancha (region of Spain), clinical data of about 2,034,921 patients was collected. The data was collected from emergency wards, inpatient and outpatient units, and primary care centers. Approximately 71,182 asthma cases were reported from January 1, 2019, to May 10, 2020. It was observed that bronchial-asthma patients infected with SARS-CoV-2 were mainly old females and had high rates of obesity, diabetes mellitus, and hypertension compared to the asthmatic patients without COVID-19. Asthma patients using inhaled corticosteroids showed lower hospital admissions. Pneumonia with the variability of radiological

expressions was the most common diagnosis in hospitalized patients. This study concluded that the incidence of SARS-CoV-2 infection in asthmatic patients was low but slightly higher in the non-asthmatic general population. Old age and related comorbidities, for example, DM and CVD, act as increased risk factors in the hospitalization of asthmatic patients with COVID-19. Whether bronchitis or asthma is an independent risk factor in COVID-19 cases is less clear. It was found that the number of COVID-19-related hospital admissions and mortalities in asthmatic patients was surprisingly low.

The impact of the COVID-19 pandemic on healthcare systems around the world has been disastrous, but children appeared relatively safe. Asthmatic children do not appear to be disproportionately affected by SARS-CoV2. There is a risk that accesses to health care, treatment, and disease control will be restricted if the pandemic persists, particularly in the poorest states. Medical care models such as telemedicine, valid questionnaires and monitoring, and cloud technology usage adoption can help improve the management of chronic respiratory diseases such as asthma. In Korea, clinical data collected from approximately 7591 COVID-19 patients reported that the mortality rate (7.8%) for coronavirus patients with asthma was quite high compared to other patients (Guan et al., 2020).

COVID-19 and severe asthma data are scary. Recently, the Belgian Severe Asthma Registry published an article. This study reported that severe asthma does not act as an increased risk factor for COVID-19 infection (Hanon et al., 2020). No doubt asthma is a highly chronic disease that has affected approximately 4.4 percent of the world's population. Asthmatic exacerbations are stimulated by respiratory viruses, increasing the infectious condition's severity (Zheng et al., 2018). Coronaviruses had triggered asthma exacerbations in the past. However, for the novel coronavirus, it is still a controversy among researchers regarding the role

of SARS-CoV-2 in asthma as a premorbid that whether it worsens the progression of the disease (Caminati et al., 2020; Richardson et al., 2020).

CONCLUSION

According to a review of the cases of COVID-19 that have been documented, people with obesity, diabetes, and hypertension are more likely to have the disease. ACE2 receptors on the pancreas and heart allow coronavirus to enter, which damages the organ, lowers blood insulin levels, and leads to diabetes and myocardial injury. Thrombosis and diffuse intravascular coagulation, which reduces PROS1 expression can lead to auto-immune disease in SARS-CoV-2 patients. Regarding the SARS-CoV-2 role of asthma as a premorbid that affects the course of the disease, there is still debate among experts in this area.

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