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REVIEW ARTICLE

The Detrimental Effect of Type II Diabetes Mellitus on Infected Patients with COVID-19

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SUMMARY

Background: **COVID-19 is no longer a global public health emergency, but it still affects numerous diseases and needs further research. Diabetic COVID-19 patients with major complications or intensive care had high mortality rates. This review provides pathophysiological descriptive data on diabetes mellitus type 2 and shows how COVID-19 infection in Saudi Arabia predicts disease severity and prognosis.**
Methods: **This review was conducted through online research on MEDLINE/PubMed databases, Scopus, and Web of Science based on links between COVID-19 and diabetes mellitus type 2 patients. By using the keywords 'COVID-19', 'diabetes', ' correlation', and impact on 'population' from December 2022 to February 2023. The full texts of the articles that were retrieved were accessed.**
Results: **The COVID-19 epidemic has affected the community, especially diabetics, and their daily life. According to our research on prior studies, most COVID-19 patients in Saudi Arabia had diabetes as a comorbidity.**
Conclusions: **We underline the necessity of thorough study to better understand COVID-19 and its association with diabetes to design and implement evidence-based initiatives and policies in Saudi Arabia, where diabetes is a major health issue.**
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KEYWORDS

diabetes, COVID-19, pandemic, mortality, comorbid diseases

INTRODUCTION

In the modern era, the intensity of diseases has increased ten-fold compare to earlier. Recently, a global pandemic was faced by the world. Individuals had unknown causes, and there was a lack of clinical procedure; this worsened the situation and clinical trials. Unusual pneumonia cases increased in Wuhan, Hubei, China, in December 2019. A deadly pathological disease

has been identified known as coronavirus disease 2019 (COVID-19) caused by a novel RNA-based SARS-CoV-2 [1,2]. This infectious virus caused huge morbidity and mortality due to the high global spreading rate. This virus was a protein, RNA-based structure (S-Protein) with spike-like projections. These projections bind with aminopeptidase angiotensin-converting enzyme 2 which mediates the transmembrane protease serine 2 (Figure 1). That helps to bind with the epithelial surface of pulmonary and alveolar cells and can spread in throughout the body cells [3]. Silent early symptoms and discrete variations may lead to a difficult diagnosis. A public health emergency was declared by WHO to control the destructive situation.

The geographically and economically largest state, Saudi Arabia, was highly affected by the COVID-19 outbreak. Recorded infected individuals were observed in the capital Riyadh. It was also the third most affected country after Iran and Iraq according to the Gulf Cooperation Council (GCC). Riyadh has the highest number of SARS-CoV2 infected residents and citizens in the country [5].

Globally COVID-19 resulted in 251,266,207 confirmed cases in which 5,070,244 mortalities were recorded in November 2021 according to WHO. Meanwhile, 7,160,396,495 vaccines administered in the same month were recorded [6]. In Saudi Arabia, 549,060 confirmed COVID-19 cases in which 8,807 deaths were reported along with 46,288,357 vaccines were administrated [7]. A high prevalence of infected individuals had preexisting comorbid diseases such as hypertension, diabetes mellitus, dyslipidemia, renal dysfunction, TB, asthma, and cardiovascular disease (CVD) [8]. In the mortality cases, 10% of COVID-19 patients with diabetes were reported from UAE. Infection with COVID-19 affects the hyperglycemia level in diabetic patients, resulting in a ten-fold increase in risk of renal failure compared to before [9]. Literature showed meta-analysis of 1,527 COVID-19 patients had DM as a comorbid disease (9.7%). Furthermore, COVID-19 patients with comorbid diseases had increased complications [10,11].

This review aims to describe the correlation between COVID-19 and diabetes mellitus type 2 and its impact role as a determinant of disease intensity and diagnosis for patients infected with COVID-19 in Saudi Arabia.

MATERIALS AND METHODS

This review was conducted through online research on MEDLINE/PubMed databases, Scopus, and Web of Science for prospective and review articles based on links between COVID-19 and diabetes mellitus type 2 patients. By using the keywords 'COVID-19', 'diabetes', 'correlation with diabetes', and impact on 'population' from December 2022 to February 2023. The full texts of the articles that were retrieved were accessed.

Diabetes and the role of angiotensin-converting enzyme 2 in diabetic patients infected with coronavirus

Globally, diabetes mellitus type 2 (DMT2) is a progressive health problem. Approximately, 25% of diabetic patients were affected by COVID in Wuhan [12]. A series of comorbidities were linked to diabetes such as retinopathy, nephropathy, neuropathy and cardiovascular upsets. Meanwhile metabolic syndrome and environmental and genetic factors also influence as the side effects of diabetes [13]. It is known that diabetic patients, especially type 2, were highly prone to numerous diseases at a time [14]. Recently, a high mortality rate was observed during the pandemic of coronavirus 2019 (COVID-19). This infection spread through droplets inhaled from atmosphere that directly affect the respiretory system [12]. Angiotensin-converting enzyme 2 (ACE2) plays a critical role in the entry of SARS-CoV-2, the virus that causes COVID-19, into human cells. ACE2 is a receptor on the surface of cells in the lungs, heart, kidneys, and other organs that allows the virus to bind and enter the cell. ACE2 is also involved in regulating the renin-angiotensin system (RAS), which is responsible for controlling blood pressure and fluid balance in the body [15].

Considering that the spike protein of SARS-CoV-2 interacts with ACE2, as does that of SARS-CoV, COVID-19 may have a pathogenic mechanism similar to SARS [4]. COVID-19 pathophysiology interacts with diabetes pathophysiology. Infection with SARS-CoV-2 can cause new-onset diabetes and severe metabolic complications in previously diagnosed diabetes, such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). Additionally, diabetes is associated with an increased risk of COVID-19 severity. In order to effectively treat COVID19, it is crucial to comprehend the clinical processes of SARS-CoV-2 infections and the therapeutic efficacy of commonly used medications in diabetic patients [16].

There is evidence that ACE2 expression may be dysregulated in diabetic patients leading to systemic infection and intense immunological reaction, which may impact the severity of COVID-19 infection [17]. Some studies have suggested that decreased ACE2 expression in diabetic patients may result in increased viral replication and a more severe disease, while others have suggested that increased ACE2 expression in diabetes may increase infection susceptibility [16].

The virus spreads and worsens the condition if the patient had a prior disease history such as diabetes type 2 and cardiovascular and renal complications [18,19]. Studies revealed that mostly diabetic patients were in COVID-19 intensive care units during the pandemic [20,21].

There is ongoing research into the relationship between diabetes, ACE2 expression, and COVID-19 infection. It is important for diabetic patients to closely monitor their blood sugar levels and take steps to maintain good glycemic control to reduce their risk of complications from COVID-19 [22].

Literature showed that the virus proliferation process increased in diabetic patients as compared to non-diabetic patients. The lack of insulin leads to increases the glucose levels that help to increase CoV2 virus replication through reactive oxygen species (ROS) which are produced by mitochondria and activate hypoxia-inducible factor (HIF)-1. Therefore, the severity of COVID-19 increases in diabetic patients which leads to death. Patients with diabetes mellitus have a higher risk of SARS-CoV-2 infection than those without, and poor glycemic control predicts an increased need for medications, hospitalizations, and mortality. SARS-CoV infection was related with a rapidly rising need for high doses of insulin in insulin-dependent patients. Changes in insulin requirements appear to be linked to inflammatory cytokine levels.

Systematic review showed 77% of diabetic, especially type 2 (DMT2), patients with COVID-19 had ketoacidosis [23]. Furin or PACE are present in high concentrations in pathological conditions; so, the requisite for SARS CoV2 virus enhanced its production which indirectly weakens the immune response and increased the viral load in diabetic patients. This load affects the lungs, kidney, heart, and renal functions which increased the mortality rate of COVID-19 patients with DMT2 [24]. Although the ROS destroyed the protein, lipid, and structure of cell, rapid destruction was observed in diabetes mellitus type 2 patients in COVID-19. Excessive inflammatory markers, i.e., D-dimer, IL-6, and ferritin, were observed in COVID-19 patients. Furthermore, microvascular and macrovascular complications were observed in diabetes mellitus patients who had COVID-19. Studies showed that T2DM mice induced with MERS-CoV had low immune status which caused severe extensive pathological effects on lungs [23].

Correlation between COVID-19 and diabetes mellitus type 2 in Saudi Arabia

Diabetes has remained one of the leading causes of growing global disease burden over the last 30 years. A systematic review of the Global Burden of Disease (GBD) from 1990 to 2019 in 204 countries found that the age-standardized, disability-adjusted life-years (DALY) rates for diabetes increased by 24.4% (185 - 297) [25].

Diabetes mellitus is a progressive disease in the modern era. Approximately half of the world population suffers from it [26]. The Middle East is the second highest and 7th highest globally. The diabetic rate was recorded in Saudi Arabia by the World Health Organization. The report showed 7 million people suffer with diabetes while more than 3 million were pre-diabetic [27]. When a review was conducted by basic and clinical science, a high prevalence of COVID-19 severity was shown in DMT2 [28] as compared to DMT1 [23]. Hyperglycemia in COVID-19 behaves as an independent predictor increasing severity leading to mortality [18,29,30,31]. Alsofayan et al., reported on results from 1,519 cases obtained from a multicenter retrospective study on COVID-19 positive patient from March 1 - 31, 2020 in Saudi Arabia, showed that 7.6% of the cases had a prevalence of diabetes, cardiovascular disease (CVD), and hypertension [32]. The descriptive study showed shortness of breath, diarrhea, fatigue, and sputum production were significant in diabetic patients, and 10.0% of 401 COVID-19 positive patients treated as non-intensive data were recorded from April through May 2020 at Riyadh hospitals, Saudi Arabia [33]. Yang in a single-center retrospective study showed 439 COVID-19 positive diabetic patients with from May through July 2020 at Riyadh Hospital [34]. According to Alguwaihes et al. 2020 had a higher prevalence of systolic pressure, cough, dyspnea, and hypothyroidism observed in diabetic patients when compared with non-diabetic patients having p-values of 0.02 and < 0.001, respectively. In 11 - 58% of diabetic patients, an 8% mortality rate were observed in COVID-19 patients [30,35]. COVID-19 positive patients with comorbid diseases showed 45.7% association especially in DMT2. Individuals over 55 years old showed 63.2% prevalence of DMT2 with 28.9% mortality rate due to COVID-19 [36]. Similarly, a recent study was based on 768 COVID-19 patients in which 76.7% were men having 96.3% comorbid diseases and 46.4% diabetic patients who were admitted to intensive care [37]. COVID-19 patients with diabetes mellitus have 52.5% prevalence among 31.3% of individuals [38]. In Qatif Hospital, 82 COVID-19 patients in which 22, 10, and 12 were diabetic, symptomatic, and asymptomatic, respectively. Mostly asymptomatic patients were diabetic 37.8% vs. 13.5% non diabetic with a significance of $p = 0.023$ [39]. In Makkah, 150 COVID-19 patients with acute respiratory distress syndrome included 53.8% prior diabetic patients admitted to ICU due to severity at al-Noor specialist hospital [40]. Research conducted at King Saud Medical City (KSMC) showed 108 individuals were selected and included COVID-19 positive patients which included 37% with prior diabetes conditions [41] (Table 1).

Are COVID-19 and diabetes mellitus type 2 in the Saudi population different from other ethnicities?

There is ongoing research on the relationship between COVID-19 and diabetes mellitus type 2 (DMT2) in different populations, including in Saudi Arabia. While some studies have suggested that DMT2 may increase the risk of severe COVID-19 illness and mortality, other factors such as age, obesity, and comorbidities can also contribute to COVID-19 severity and outcomes [42].

In terms of differences between ethnicities, there is some evidence to suggest that certain populations, including those of South Asian, African, and Hispanic descent, may have a higher risk of developing DMT2 compared to other ethnic groups. However, the prevalence of DMT2 in Saudi Arabia is relatively high, estimated at around 17% of the population, and there may be unique factors in the Saudi population that contribute to this, such as genetic and lifestyle factors. [43].

Table 1. Total percentile of COVID patients incidence of Diabetic Patient (%) in Intensive care along with Mortality rate.

COVID Patients No.	Diabetic patient (%)	Intensive care (%)	Mortality rate (%)	Ref.	Comments
439	68.3	17.9	2.8	Alguwaihes et al. 2020	DM patients have a higher mortality rate than their non-DM counterparts
1,519	5	4.7	0.65	Alsofayan et al. 2020	Reported 7.6% of the cases have a prevalence of diabetes & reported mortality in less than 1% of the cases. This does not reflect the final outcomes of the entire study population.
1,576	11 - 58	3.5	8	Yang J, et al. 2020	The most common factors behind COVID-19 mortality are older age and concomitant disease.
300	45.6	100	10	Sheshah E et al. 2021	COVID-19 positive patients with comorbid diseases showed 45.7% association, especially DMT2. Individuals above 55 years old showed 63.2% prevalence of DMT2 with 28.9% mortality rate due to COVID-19
768	46.35	45.8	11.5	Abohamr et al. 2020a	Found that ICU admission was significantly associated with diabetes mellitus ($p = 0.001$). Clinical predictors of death were: obesity ($p = 0.001$), history of smoking ($p = 0.001$), and diabetes mellitus ($p = 0.001$)
99	31.3	22.2	12.1	Barry M et al. 2020	Patients ≥ 65 years old had high mortality ($p < 0.001$), and the most common comorbidities were hypertension (43%) and diabetes (42%).
82	26.8	4.87	75	AlJishi et al. 2021	Comorbidities were present in 50% of patients in study populations, hypertension in 27%, and diabetes mellitus in 26%
150	26	10.7	12.5	Shabrawishi M, et al. 2020	The most common comorbidities were hypertension (28.8%, n = 42) and diabetes mellitus (26.0%, n = 38)
108	37	16.6	5	Abohamr et al. 2020b	Of 108 individuals were selected having COVID-19 positive patients 37% suffered from prior diabetes conditions

It is important to note that the relationship between COVID-19 and DMT2 is still being studied, and the impact of these conditions may vary depending on individual factors and comorbidities. It is essential for individuals with DMT2 to follow guidelines for reducing the risk of COVID-19 transmission and to manage their condition through proper treatment and lifestyle modifications. [44].

Hospitalization of COVID-19 diabetic patients

A comprehensive study and management strategy is needed to identify the risk factors to treat two complicated diseases at the same time. The International Diabetes Federation (IDF) reports that 4,275,200 Saudi individuals were diagnosed with diabetes and the majority had pre-diabetic conditions. COVID-19 was an alarming situation all over the world, but the severity was increased for type 2 diabetic patients. Therefore, Riyadh city was more affected by these pandemic situations in which a high mortality rate of COVID-19 positive diabetic patients was observed (risk factors for hospital admission among COVID-19 patients with diabetes). Somehow, it gives a limited impression of COVID-19 effect on diabetic patients, but the bidirectional association of DM and COVID-19 had been suggested by researchers. Their studies showed that hospitalization increases the risk of severe illness and leads to death in COVID diabetic patients [45,2].

Literature showed a retrospective study in which independent association with hospitalization and HbA1c values showed a high tendency to developing severe COVID-19. In this study, 48% of patients were analyzed on the basis of independent association with 70 - 79 years ($p = 0.017$) and ≥ 80 years ($p = 0.001$). Furthermore, the patients who take insulin treatment must face complications related to COVID and hospitaliza-

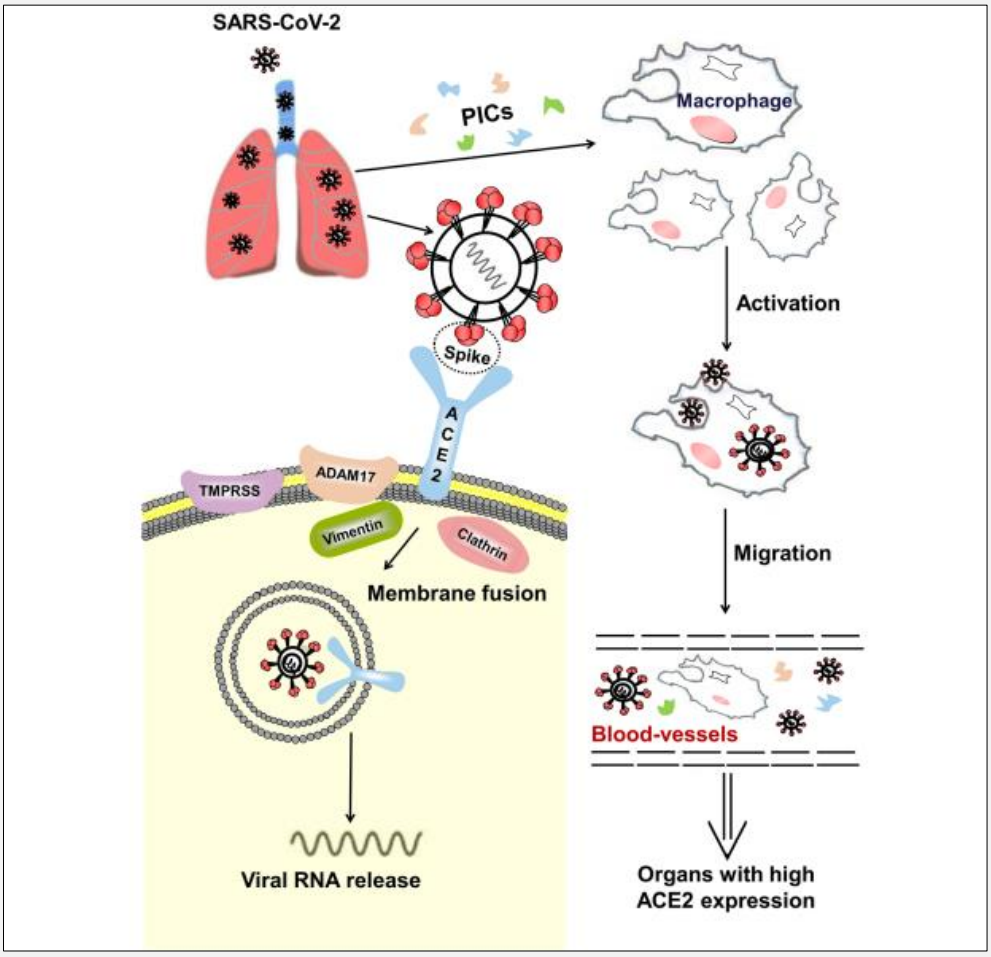

Figure 1. A model for the process of SARS-CoV-2 entering host cells in the lungs and attacking other organs. SARS-CoV-2 enters the lungs, where the spike glycoprotein of the virus binds to ACE2 on cells, allowing the virus to enter the cells. Some transmembrane proteinases, such as transmembrane protease serine 2 (TMPRSS2) and a disintegrin metallopeptidase domain 17 (ADAM17) also participate in this process. For example, SARS-CoV-2 can use TMPRSS2 for spike protein priming in cell lines. The infected cells and inflammatory cells stimulated by viral antigens can produce pro-inflammatory cytokines (PICs) and chemokines to activate immunological reactions and inflammatory responses to combat the viruses. Cell-free and macrophage-phagocytosed viruses in the blood can be transmitted to other organs and infect ACE2-expressing cells at local sites [4].

tion under these circumstances. The literature showed that 27.6% of diabetic patients were in intensive care just because of their ongoing insulin therapy which indirectly affects the kidney, lungs, and heart to an acuter level such as heart attack, renal failure, and respiratory distress. Acute hyperglycemic crises lead to ketoacidosis or a hyperosmolar hyperglycemic state, which could also be triggered by COVID-19. The ratio of mortality of diabetic patients with insulin therapy in COVID was 51.7% as compared with non-insulin therapy diabetic patients at 3.6% [46]. Another retrospective study showed 91 out of 485 COVID patients were diabetic. The proportionality of diabetic patients in severe cases was highly significant compared to non-severe ($p < 0.001$). In this situation, the mortality rate increases up to 40.04% in the severe group [47].

Effect of corona virus infection in the mortality rate among diabetic patients

The mortality rate for diabetic patients infected with coronavirus (COVID-19) varies depending on several factors, including age, overall health, and comorbidities [34].

Several studies have reported mortality rates for diabetic patients with COVID-19. A study published by Chandrasekaran et al. in 2021 found that the mortality

rate for diabetic patients with COVID-19 was 9.5% [48], and according to a report by the Centers for Disease Control and Prevention (CDC), people with diabetes are at higher risk of severe illness and death from COVID-19 than people without diabetes. The report also noted that the risk of death was higher for people with poorly controlled diabetes.

In another study, Riddle MC reported a mortality rate of 14.8% for diabetic patients with COVID-19 [49].

It is important to note that these mortality rates are averages and may not reflect an individual's risk. The best way for diabetic patients to protect themselves from COVID-19 is to follow the recommended guidelines for preventing the spread of the virus, such as wearing masks, practicing social distancing, washing hands frequently, and getting vaccinated when possible [19].

However, according to a study by Sindi et al., the mortality rate for diabetic patients infected with COVID-19 in Saudi Arabia was found to be 26.5% [50]. It is important to note that mortality rates can vary depending on many factors, such as age, overall health, and access to healthcare, and may have changed since the publication of the study.

Elderly diabetic patients have a high probability of death. Many risk factors include heart failure, smoking, β-blocker use, bilateral lung infiltrates, raised creatinine levels, and vitamin D deficiency, which are significant predictors of mortality. Literature showed a significant mortality rate in the diabetic group with a short survival time as compared to the non-diabetic group in intensive care [34,50]. Diabetes is not only associated with mortality but also with other acute or chronic preexisting conditions which worsen in COVID infections. HbA1c levels were also led to adverse outcomes of COVID-19. Similarly, a multi-center retrospective study in Wuhan reported 1,561 COVID-19 patients with the presence of diabetes as not associated with in-hospital mortalities.

In the US, a lack of association between DM and mortality was reported among 463 COVID-19 patients admitted to ICU on ventilators. Meanwhile, one-third of COVID-19 patients had mortality from having pre-existing diabetes in hospitals. Major risk factors were poor prognosis and undefined treatment of diabetic patients suffering from COVID-19. However, it was also suggested that the COVID treatment showed side effects in the presence of diabetes in patients that are lethal to health and severity plus other complications lower the immunity of the body that leads to death. [34].

CONCLUSION

The COVID-19 pandemic has had a significant impact on the community, particularly diabetics, and their daily lives. In Saudi Arabia, most studies have indicated diabetes as one of the most common comorbidities among COVID-19 patients, according to our research on previous studies. As diabetes is one of the major health issues in Saudi Arabia, we emphasize the importance of conducting comprehensive research to gain a better understanding of COVID-19 and its relationship with diabetes in order to develop and implement evidence-based programs and policies in the country.

Declaration of Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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