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The relationship between diabetes mellitus, psychological stressors and COVID-19 challenges and managements: An evidence-based literature review

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***Abstract*---**Background: COVID-19 outbreak is likely to cause psychological problems, such as anxiety, depression, and stress; which may negatively influence one's glycemic control. The pandemic could increase the prevalence and change in nature of diabetes among people living in countries affected by it. The aim of this review is to clarify the blurred areas and types of relationship between diabetes, psychiatric disorders, and COVID-19 pandemic. Methods:_Literature reviews and evidence-based researches were studied using PubMed and Google Scholar for the following keywords: "COVID-19", "SARS-CoV-2", "diabetes", "epidemiology", "pathophysiology", "ACE2", "manifestation", "immune system", "link between diabetes and psychiatric illnesses", and "treatment with antipsychotics and antidepressants". Results revealed that there is a casual mutual relationship between DM and psychiatric disorders. Furthermore, there is a bidirectional relationship between DM and the vulnerability of acquiring COVID-19 infection. Additionally, DM and SARS-CoV-2 infection worsen each other, thus, diabetics are more likely to develop severe COVID-19. Conclusion and Recommendation: It is recommended that physicians and health care providers counsel their

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patients that the risk of DM can be significantly reduced by lifestyle changes including diet and exercise. Additionally, a range of psychological interventions, and mandatory vaccinations against COVID- 19 when dealing with diabetic patients.

***Keywords*---**Diabetes, Psychiatric, Relationships, COVID-19, literature.

Introduction

Stress hyperglycemia and diabetes are common in the hospital's setting, and are linked to increased hospital complications and mortality during the pandemic of COVID-19. The pandemic showed that people with diabetes are five times more likely to develop complications in the hospital than people without. Starting from December 2019, a new virus (Coronavirus), believed to cause acute respiratory syndrome, emerged from Wuhan in the Hubei province of China. In the beginning, the virus was known as "Severe Acute Respiratory Syndrome Coronavirus-2" (SARS-COV-2). Then, the World Health Organization (WHO) in February 2020 gave the disease the new name COVID-19 [1]. Ever since the beginning of the pandemic, significant challenges and concerns in patients with a preexisting chronic condition, such as diabetes and cardiovascular disorders, were faced [2]. COVID-19 tends to spread rapidly and sustainably from one person to another, which caused a global health crisis, and has negatively impacted the social, economic, and political aspects of life. SARS-COV-2 has been actively eradicated by clinicians, health professionals, scientists, organizations, and governments by sharing their experiences and knowledge.

WHO's Technical Advisory Group on Virus Evolution (TAG-VE) designated variant B.1.1.529, a variant of concern on 26 November 2021, calling it Omicron. The decision was made on the basis of evidence presented to the TAG-VE that Omicron has several mutations that may impact its behavior, such as how easy it can spread or the severity of its illness. Several international research teams are conducting studies to better understand many aspects of Omicron and will be sharing their findings as soon as they are available. Compared to other variants of concern, there may be an increased risk of reinfection with Omicron (i.e. people who previously had COVID-19 may get infected more easily with Omicron), but the evidence is limited. Therefore, WHO is working with researchers around the world together to better understand Omicron. Researchers and ongoing studies are assessing transmissibility, severity of infection (including symptoms), and effectiveness of vaccinations, diagnostic tests, and treatment.

Aim of this review:

The current literature review aims at searching all evidence-based researches to identify the relationship between Diabetes Mellitus (DM) and COVID19, as well as the challenges and managements used to decrease the impact of the pandemic.

Methods:

To address this, the current knowledge on COVID-19 in the Western Pacific, including the epidemiology, virology, impact of diabetes on COVID-19, and treatment of COVID-19 as well as the standard of care for diabetic patients during this very critical time were searched. From December 2019 to early January 2022, PubMed and Google Scholar were searched for the following keywords: "COVID-19", "SARS-CoV-2", "diabetes", "epidemiology", "pathophysiology", "ACE2", "manifestation", "immune system", "link between diabetes and psychiatric illnesses" and "treatment with antipsychotics and antidepressant". Literature review and evidence-based researches were searched to answer the following research questions:

1. What are the epidemiological characteristics and complications of diabetes mellitus?
2. What is the psychopathology of stressors during COVID- 19 and its association with DM?
3. How DM can lead to psychiatric disorders?
4. What are the psychiatric disorders associated with DM?
5. What is the relationship between atypical antipsychotics and DM?
6. What is the role of vaccination and life style modifications in decreasing the challenges faced by DM patients?
7. How will diabetes and COVID- 19 be treated in the future?

I. Epidemiological characteristics of diabetes:

According to the World Health Organization (WHO), the estimated ratio of the global diabetes prevalence in 2019 is 9.3% (463 million people), increasing to 10.2% (578 million people) by 2030 and 10.9 % (700 million) by 2045 [3]. In addition, WHO has reported that Saudi Arabia ranks as the seventh in the world and the second highest country in the Middle East for diabetes rate [4].

Although, the epidemiological studies showed that the prevalence of patients with diabetes affected by COVID- 19 wasn't different from the prevalence of diabetes in the general population, however, diabetic patients hospitalized with COVID-19 risk a higher mortality rate as well as higher rate of progression to acute respiratory distress syndrome [2]. In addition, Orioli, et al [1] stated that both patients and their caregivers face multiple challenges to ensure continuity of care and to prevent the risks related to their pre-existing chronic conditions such as DM.

In patients with long-term DM and hyperglycemia, innate immunity is compromised, resulting in elevated severity of infection. Innate immunity protects us from infections, especially viruses such as COVID-19. The presence of diabetes was a significant predictor of the severity of illness in 174 patients with COVID-19 from China. Diabetic patients who contract COVID-19 are more likely to develop adult respiratory distress syndrome (ARDS), pneumonia, a hypercoagulable state, and excessive uncontrolled inflammation [5-7]. The severity of the illness can also be increased due to viral intrusion. COVID-19-related adverse outcomes and mortality [8 & 9] will present as a major comorbidity for people with diabetes (type 1 and type 2). In September 2020, Canada's Public Health Agency reported data

indicating that people with diabetes were more likely to be hospitalized with serious illness than in other countries. Moreover, Ojo, [10] reported that Diabetes Mellitus (DM) presents a major public health challenge despite the developments in technology and the pharmaceutical industry.

Diabetes Mellitus diagnostic criteria and complications:

Diabetes mellitus is a metabolic condition that is characterized by chronic hyperglycemia and results from reciprocal influence between genetic and environmental factors [11]. There are four criteria for diagnosing diabetes mellitus: 1) fasting plasma glucose level of 7.0mmol / L, 2) plasma glucose level of 11.1, 3) casual plasma glucose level of 11.1, and 4) glycated hemoglobin level of 48mmol / mol. [12]. In this regard, the initial term 'diabetes' is derived from the ancient Greek word 'diabainen', which means 'go through', to indicate the excessive urination (polyuria) that was historically considered as the main diagnostic characteristic. Then Willis on 1600s added the term 'mellitus' (sweet) to differentiate between excessive urination from diabetes mellitus and excessive production of non-sweet urine associated with diabetes insipidus [13]. As it was reported in many literature reviews, every year the incidence of diabetes was assessed based on the American Diabetes Association (ADA) diabetes criteria: such as fasting plasma glucose level of 126 mg per dL or greater, or a two-hour plasma glucose level of 200 mg per dL or greater, or Hemoglobin A1c (HbA1c) level of 6.5% or greater [14]. However, blood glucose level testing should be repeated on a subsequent day to confirm the diagnosis [15 &16]. Zaccardi, Webb, Yates, Davies, [13] stated that T1-DM is currently well-recognized as an autoimmune disorder characterized by pancreatic β-cells destruction, while T2-DM results from inadequate insulin secretion due to pancreatic β-cells dysfunction, insulin resistance (IR) and an inadequate compensatory insulin secretory response associated with increased caloric intake. As a result, the imbalance in glucose homeostasis and hyperglycemia are considered the main characteristics of T2DM [17]. The epidemiological data shows that over 90% of patients with T2DM are associated with the global increase in obesity, sedentary lifestyles, and high caloric intake. Being obese or having high percent of adipose tissue promotes IR through various inflammatory mechanisms [18]. The clinical signs and symptoms of diabetes depend on the blood glucose level. The classic clinical features of all types of diabetes include polyuria, polydipsia, and polyphagia, the "three Ps", in addition to unexplained weight loss. Polyuria means, increased urination, while polydipsia means increased thirst that occur as a result of the excess loss of fluid associated with hyperglycemia, and polyphagia in which the patients experience increased appetite. Other symptoms include weakness, fatigue, sudden vision changes, numbness or tingling in hands or feet, recurrent infections, dry skin, and skin lesions that are slow to heal [19-20].

Diabetic people who have COVID-19 have a higher likelihood of developing complications. Approximately two thirds of the deaths associated with COVID-19 in Italy have been observed in diabetic patients. Similarly, diabetes and mortality have been connected in the previous epidemics caused by coronaviruses, such as that caused by SARS in 2002 and the Middle East Acute Respiratory Syndrome (MERS) in 2012. In addition, SARS-CoV-2 has been shown to cause diabetes in

patients who have contracted it as the virus might alter glucose metabolism, causing diabetes mellitus.

Kharroubi,& Darwish, [12]stated that early diagnosis of diabetes and prediabetes is necessary to decrease complications. Thus, screening for diabetes is essential especially before signs and symptoms develop, leading to earlier diagnosis and treatment. People should be assessed for clinical manifestations of diabetes as well as glucose levels [21].

II. What is the psychopathology of stressors during COVID- 19 and its association with DM?

A newly emerging study has shown that T2-DM and COVID-19 are bidirectionally correlated. Firstly, preexisting diabetes increases the risk of poor outcomes and death after COVID-19 [22-24]. These findings could be explained by various factors. Diabetic patients are at high risk of developing diseases because their innate immune system is compromised as well as their adaptive immune system [25]. Infection with COVID-19 results in a significant reduction of natural killer cells, notably CD4+ and CD8+ cells, as well as CD4+ and CD8+ lymphocytes [26], which are the main cells responsible for fighting off infections.

In this regard, researchers still do not know how these very recent findings work: whether they are a result of interactions between the virus and beta cells or target tissues for insulin action, or a result of an indirect immune response ("cytokine storm"). A possible explanation for the correlation between COVID-19 and hyperglycemia in patients with T2D [27] may lie in metabolic inflammation and exaggerated cytokine release, which might lead to suppression of insulin (produced by beta cells) and glucagon (produced by alpha cells) secretion. The important role of both insulin and the glucagon is to maintain a constant level of glucose in the blood [28 &29]. Interestingly, a recent report [30] describes the increased expression of ACE2 protein and mRNA in human beta cells upon exposure to inflammatory cytokines, presumably resulting in greater vulnerability to infection and glycemic index decline, which is seen in patients with preexisting T2-DM during COVID-19.

Recent data suggest that infection with SARS-CoV2 can worsen glycemic control, resulting in severe insulin resistance (50-100 U insulin/hour) and impaired insulin secretion, both of which can lead to diabetic ketoacidosis, DKA. The occurrence of severe DKA with COVID-19 has been observed frequently upon admission to hospital [31], which contributes to mortality and morbidity.

III. Prevalence of mental disorders among diabetic patients during COVID-19

It is well-known that psychological problems and diabetes mellitus will often interact; the challenges of living with and overcoming diabetes may result in emotional overload. The prevalence of depression and anxiety symptoms among diabetic patients is twice as high as that of the general population [32& 33], which is may be associated with poor adherence to treatment, resulting in worse blood glucose control [34& 35]. According to Meurs et al., [36] a study of more

than 90,000 patients found that patients with diabetes had an 80% greater likelihood of depression and anxiety [37& 38]. Literature data demonstrate that depression and diabetes co-occur at a rate between 17.6% and 21% [39& 40]. While there is still much work to be done to fully understand the relationship between diabetes and depression, it is evident that metabolic dysregulation can influence brain function, such disturbances in glucose regulation may lead to depression [41& 42]. In addition, there might be a link between depression and low levels of insulin-like growth factor (IGF), which was shown in experimental studies to produce antidepressant effects. Therefore, diabetic patients tend to experience high psychological responses [43]. Accordingly, a stressful environment could exacerbate diabetes-related mental health conditions and result in adverse diabetes outcomes [44& 45].

According to researchers, the COVID-19 outbreak is likely to cause psychological problems, such as anxiety, depression, and stress, to increase in prevalence and change in nature in the countries affected by the pandemic [38,46, &47]. COVID-19 was found to have an important psychological impact during the outbreak in China, with half rating it as moderate or severe; 17% reported moderate to severe depressive symptoms; 29% reported moderate to severe anxiety symptoms; and 8% reported moderate to severe stress levels [48]

Researchers found that people with chronic illnesses were more likely to experience stress, anxiety, and depression than those without [48]. Recent studies indicate that depression is as prevalent among Arabian patients with diabetes as it is in other countries such as Brazil, USA, China (35% anxiety and 20% depression), and with a prevalence of 22% in many studies published since the beginning of the pandemic. Additionally, according to Alessi et al., [49] and Gunnel et al. [50] psychological distancing by COVID-19 may also increase suicide risk in patients with diabetes. Besides, Moradian et al., [51] according to their study results, after the initial COVID-19 outbreak, depression symptoms, generalized anxiety symptoms and distress have increased, and health status of diabetes patients has decreased significantly. It is likely that the high prevalence of psychological distress observed was influenced by the fact that health appointments were not fully available, challenges in getting medicines and supplies, as well as the poor understanding of the connection between diabetes and psychological distress, all of which seem to have exacerbated the vulnerability of diabetics. In fact, pandemic- related mental health problems are likely to persist longer and peak later than the actual epidemic [Gunnell et al., [50] and [Khalil, [52]. Therefore, in a time when policy task forces are crucial, mental health professionals should be active and involved during this critical time [53].

IV. The bidirectional link between diabetes, psychological disorders and COVID-19

A common feature of many species is that they have two major immune subsystems: the innate immune system and the adaptive immune system. Both subsystems rely on humeral immunity and cellular immunity to function. During the aging process, the peripheral immune system and the neuro-immune system, which protects the brain, are separated by the blood-brain barrier. Once this

barrier is broken, the peripheral immune system and the neuro-immune system attack. Whenever stressed, our immune system has a difficult time fighting off foreign substances. Consequently, becoming more vulnerable to infections. It has been observed that the brain perceives a stressful situation by activating the HPA axis and the sympathetic-adrenal medullary axis (SAM), which activates the release of various immune-modulating hormones, including adrenocorticotropic hormone (ACTH), cortisol, growth hormone, prolactin, epinephrine, and norepinephrine. It is known that stress hormones can suppress the effectiveness of the immune system. As a matter of fact, it was reported that depression, hopelessness, and avoidant-coping mechanisms are significantly associated with a faster decrease in CD4 count and increased viral load, demonstrating an evident effect of stress on the immune system and the progression of viral and inflammatory diseases [54] Furthermore, studies have confirmed that negative emotions, including anxiety and depression, can modulate the antibodies and t-cells that respond to vaccines against viral infections [55 & 56].

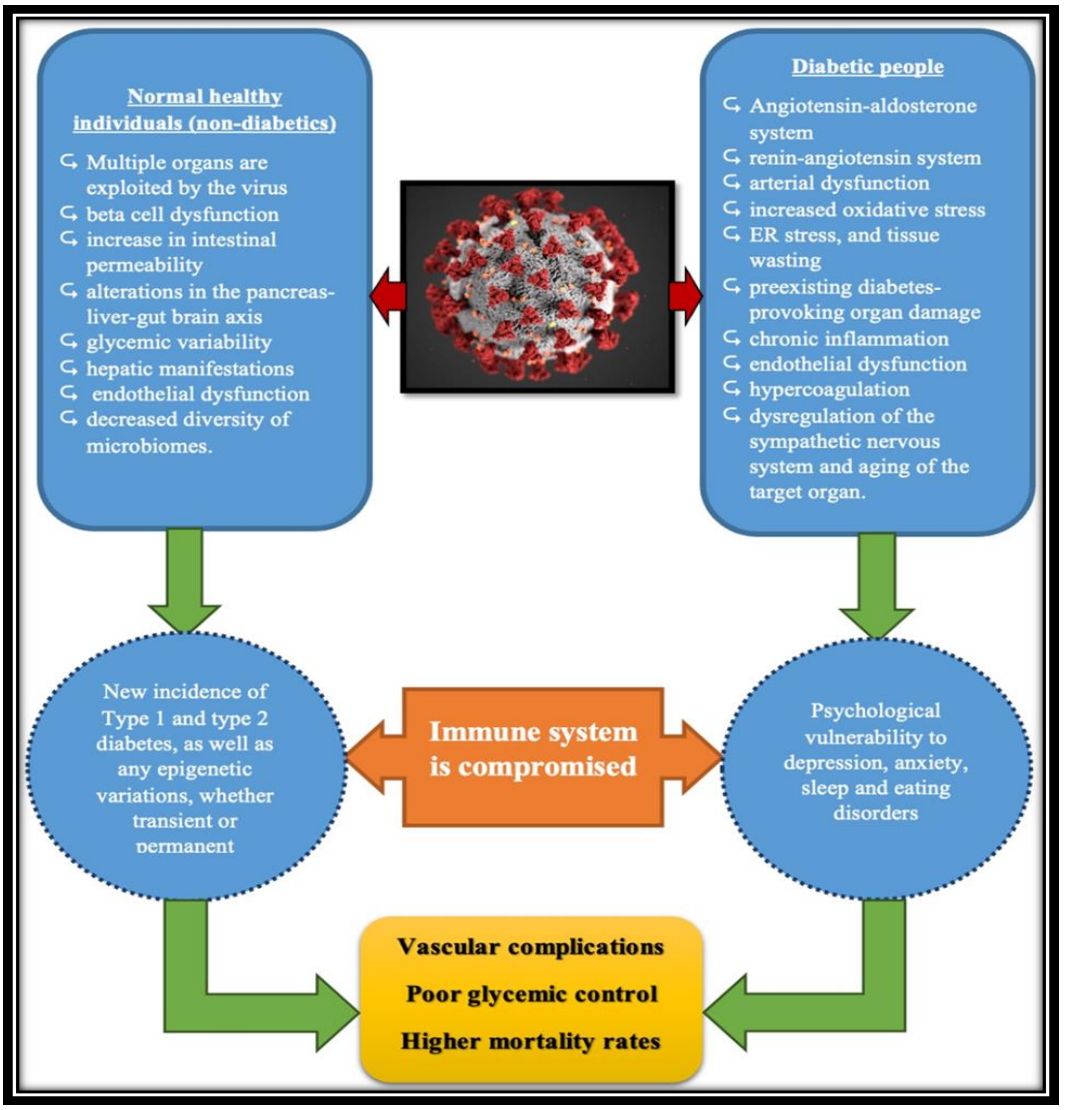

Figure (1) The Bidirectional Relation Between Diabetes, Psychological Disorders and COVID 19

Angiotensin-converting enzyme 2 (ACE2) is activated by SARS-CoV-2 infection and results in an increase in reactive oxygen species (ROS) that promote cytopathic hypoxia. Hypoxia triggers the release of pro-inflammatory cytokines through the production of free radicals, resulting in endothelial derangement and increased coagulability. Additionally, free radicals are produced by macrophages and neutrophils when pro-inflammatory cytokines are elevated. Similarly, patients with diabetes mellitus who are infected with COVID-19 often have adverse outcomes due to oxidative stress. COVID-19 is characterized by a severe inflammatory state in the lungs due to neutrophils, which triggers the production of cytokines, eventually leading to hypercoagulable state in the same way (Fig. 1). The excess production of superoxide in T1DM results in endothelial dysfunction, which produces pro-inflammatory cytokines. The destroyed endothelial cells

release coagulation factors and adhesion factors. Hyperglycemia, by activating the protein kinase C (PKC) pathway, leads at the same time to an increase in adhesion molecules, contributing further to endothelial dysfunction, resulting in platelet aggregation and activation.

V. Psychiatric disorders and psychotropic link with diabetes

Uncontrolled hyperglycemia can lead to multiple complications such as diabetic retinopathy and diabetic nephropathy, that may cause blindness, and kidney failure as well as increases the risk of cardiovascular diseases [57]. Additionally, approximately 30% of diabetics suffer from mental disorders, such as depression, schizophrenia, delirium, and substance abuse (such as tobacco smoking). There is a known association between depression and diabetes, as well as an increased prevalence of diabetes in people with schizophrenia. Mukrim, et al., [58] stated in their study about depression, anxiety and stress among diabetes mellitus patients in Arar, Northern Saudi Arabia that the prevalence reached approximately 45.6% for anxiety, 18.7% for stress, and 37.4% for depression among diabetic patients. Also, they concluded that anxiety, stress, and depression are common psychiatric disorders that often affect people with chronic illnesses specially diabetes. The phenomenon can be explained in two ways. A combination of diabetes mellitus, antidepressants and antipsychotics can result in metabolic abnormalities. Patients with diabetes mellitus are therefore at greater risk of psychiatric disorders. The most metabolic abnormalities are caused by antidepressants with noradrenergic activity. It has been shown that clozapine and olanzapine pose the highest risk of diabetes, risperidone and quetiapine present a moderate risk, while ziprasidone and sertindole do not pose a risk. Therefore, it is important to monitor weight gain monthly during the first three months, then to perform biochemical analysis every three months, and then once a year afterwards. The first intervention should be switching to another antipsychotic in patients with significant weight gain, an increase in blood sugar level, or dyslipidemia. An endocrinologist should be also consulted if necessary, so that lifestyle changes can be recommended.

As regard to the effect of covid 19 on increasing the prevalence of covid 19, In many countries, social programs are being implemented such as distancing which has led to a significant change in national attitudes, behavioral patterns and shut downs of daily functions. The effect of this could slow the spread and flatten the curve of other diseases, but the consequences on mental health are unknown and unrecognized [52]. Nevertheless, it has been demonstrated that large-scale disasters of all kinds, whether traumatic, natural or man-made are accompanied by some kind of increasing the prevalence of depression and posttraumatic stress disorder, substance abuse disorders, and many others [52]. Accordingly, in their systematic and meta-analysis survey report, Pappa, Ntella, and Katsaounou [59] found: Anxiety prevalence from 12 studies was 23.2%, and depression prevalence from ten studies was 22.8%. In addition to this, another study by Huang and Ning Zhao [63] found that younger people reported higher levels of GAD symptoms and depressive symptoms than those over the age of 50. Therefore, many studies concluded that covid 19 with its restrictions and precautions lead to increase the prevalence of mental disorders among young as well as old people.

VI. What is the role of vaccination and life style modifications in decreasing the challenges faced by DM patients?

Diabetes is an epidemic affecting the lives of entire families, as well as severely burdening the healthcare system and as per all evidence research. The number of cases of diabetes is expected to increase to 380 million globally by 2025, and to 552 million by 2030 in the next decade [8]. These figures do not include undiagnosed diabetics, which are approximately 183 million people. Currently, scientists are striving to find treatments that can cure this chronic disease. According to research studies, diabetic patients become more actively involved in the therapeutic process after suffering from medical complications from uncontrolled diabetes [59].

In terms of controlling the spread of COVID-19, several preventive measures have been taken from all national and international agencies. These include developing different types of vaccines such as Pfizer and Biontech, Moderna AstraZeneca, Sinovac biotech and many other trials are still under investigations. Additionally, all governments require that all citizens follow the international precautions of quarantine, isolating suspected cases, tracking contacts, monitoring them, and distributing regional and national information, which includes suggesting that diabetes patients do not engage in high-risk activities. Khalil, Nasr and Enar [62] and Gupta, et al [63] recommended that targeted immunotherapy meets with drug resistance patients (diabetics) easily and has narrow treatment windows, making it an alternative to some antivirals. SARS*induced lung injury cases were linked to an inflammatory response of the body in 2003, where glucocorticoids were used in the treatment of SARS to control pulmonary infection. Therefore, it is important in pneumonia cases of COVID19 to control the level of cytokines and inflammatory molecules, as they are thought to be responsible for the accumulation of cells and fluids. In response to expert advice and clinical evidence, the US National Institutes of Health (and the World Health Organization) outlined recommendations for optimum COVID-19 patient care. [64]

There is a need for continuous glucose monitoring in diabetic patients with COVID-19 even if they are not critically ill [65]. It is important to delineate COVID-19 patients with comorbidities and those without from the time of admission to the hospital.134 Patients with comorbidities and those without must be treated separately, and tips must be tailored specifically for individuals with these conditions. [66] The adherence to personal care routines should be particularly strict for COVID-19 patients with comorbidities, especially physical/social distancing and handwashing. As part of the prevention of COVID-19 infection, diabetic patients must increase their metabolic control as necessary. Due to the low immunity among people with comorbidity, it is recommended that if a patient has minor symptoms that can be managed at home, they should remain isolated. [67] Influenza vaccination reduces pneumonia risk by 43%–55% among people with DM, and may be used to differentiate symptoms of COVID-19 from influenza. A doctor's consultation is also essential for managing COVID-19 infection in patients with comorbidities [68]. Sardu et al [69] found that patients with COVID-19 had a reduced risk of serious conditions, such as heart attacks, if they maintained optimal glucose control during admission. COVID-19 patients

with hyperglycemia are at higher risk for severe disease during hospitalization especially those treated with tocilizumab, an IL6 inhibitor, where there is an over activation of innate immunity leading to poorer outcomes from COVID-19 infection [70]. According to these findings, early management of hyperglycemia may help to reduce adverse outcomes among hospitalized hyperglycemic COVID-19 patients [71].

Typically, DM patients also tend to have dyslipidemia and hypertension as well as other metabolic disorders. Accordingly, continuous treatment is useful for people with DM to lower their lipidemic index, eventually controlling hypertension and lowering the risk of acquiring infections.

It is possible that SARS-CoV2 damages ACE2- and Mas1-receptor pathways, which act as protective mechanisms against lung injury caused by COVID-19. Accordingly, COVID-19 patients reported significantly reduced mortality and hospital stays with the use of ACEI and ARB prescriptions. [69 & 70] In studies, the European Society of Cardiology, American Heart Association, and Heart Failure Society of America suggest that T2DM patients should continue taking antihypertensive medications, including Angiotensin-Receptor Blockers and Angiotensin-Converting Enzymes (ACEIs and ARBs) [71 &72]. Furthermore, drugs such as statins can fix this problem. The anti-inflammatory effects of statins play an important part in upregulating ACE2.146 ACE2 is reduced by high levels of lipids, such as low-density lipoprotein [73]. Due to the close association between CVD and DM, researchers recommended controlling lipids in COVID-19 patients [74].

Additionally, many medications are currently available to treat hyperglycemia, with different mechanisms of action and targeting different pathophysiological components of the disease, such as “Metformin, Sodium–Glucose cotransporter 2 (SGLT2 inhibitors), Dipeptidyl Peptidase-4 (DPP-4 inhibitors), Glucagon-Like Peptide 1 (GLP-1 receptor agonists), peroxisome proliferator–activated receptor g agonists” such agents are not always able to achieve adequate control unless they are started earlier in disease progression or are used in combinations [75 & 76].

In addition, COVID-19 is highly prevalent among health-care professionals with DM who provide care for COVID-19 patients. It is therefore crucial that these workers use high-level safety protocols whenever possible [71&77]. Dorjee et al [78] proposed that adhering to proper treatments for modifiable risk factors, such as diabetes and hypertension, could decrease mortality and morbidity among patients who contract COVID-19.

Lifestyle modifications for both COVID- 19 and diabetes:

Numerus studies reported that up to 90% of T2DM cases could be prevented if individuals follow a healthy lifestyle. In this regard, lifestyle modification (physical activity, weight loss and a healthy diet) is considered as the first-line treatment of hyperglycemia. Exercise has been shown to improve blood glucose, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being [79]. The recommended exercise for adults over age 18 years engage in 150 min/week of moderate-intensity (such as Brisk walking, Cycling, and Hiking) or 75

min/week of vigorous-intensity aerobic physical activity (such as Jogging, Swimming, Football and Gymnastics) [80].

Epidemiological studies suggest that high versus low total physical activity is associated with a decrease in diabetes risk by 30% approximately [81]. In this regard, body weight management is important especially for overweight and obese people with diabetes, as it may reduce the risk of developing diabetes and can enable people with pre-diabetes or type 2 diabetes to control blood glucose levels [80]. Also, according to National Institute for Health & Care Excellence (NICE) guideline, it is recommended for the overweight patient to lose weight gradually until a healthy BMI (18.5 to 24.9) is achieved, with a target to reduce weight by 5% to 10% over a period of a year [82]. In addition, various research confirmed the importance to personalize physical activities (PA) for diabetic patients according to their goals, health status, physical condition, and exercise responses. Patients who are unwilling or incapable of performing PA as recommended, can still benefit from exercising at lower levels or reducing the total time engaged in sedentary activities such as sitting for long periods, watching television, using computers or mobiles, riding in a bus or car, …. etc [82].

Although PA is of a great importance, but the fear of hypoglycemia is a one of the main challenges while performing it regularly. So, prevention of hypoglycemia during and after PA remains an important issue in the management of DM [83]. In this regard, diabetic patients should start PA gradually then increase it daily or weekly; for example: starting with 10-minute periods of low or moderate physical activity to more intense activity in order to achieve their targets goals [84].

Another lifestyle changes for diabetic patient is to be compliant to a healthy diet. The most successful nutritional strategy for DM prevention and management is to consider the individual culture, personal preferences, and food availability to follow the recommended diet. This can be achieved by using a variety of food from the different five main food groups every day [85]. Moreover, the diet should provide the patient with adequate amounts of nutrients and kilojoules to maintain healthy weight, stabilize levels of blood glucose, maintain lipid level within normal range and prevent or delay diabetic complications [80].

In addition, the current dietary guidelines for both T1DM and T2DM have no big differences between both of them. For example, high quality of carbohydrate sources (as whole grain, legumes, vegetables and fruit) is preferable. Also, it is important to count carbohydrates intake and consider the type and amount of PA to help in adjusting insulin therapy accordingly [86]. Regarding the intake of protein, a study comparing 15% vs. 30% energy from protein, noted that the improvements regarding insulin requirements, fasting glucose and weight in the group that consumed 30% energy is better than the group who consumed 15% energy from protein [87].

Ojo [10] stated that there was a randomized controlled trials that studied the effect of polyunsaturated fatty acids (PUFAs) on glucose level in people with DM. The research concluded that high intake of PUFAs decreases the risk of DM by reducing level of blood cholesterol, preventing cardiovascular diseases and affect

insulin sensitivity. In addition, according to dietary guideline of American diabetes association (ADA) it is recommended for diabetic patients to use the unsaturated fatty acids instead of saturated fatty acids [88].

Multiple clinical studies further showed that sucrose “table sugar” has more effect on glycaemia than equal caloric intake from starch. So, it’s important to avoid excess intake from nutritive sweeteners. On the other hand, non-nutritive sweeteners were found to be safe when used within acceptable daily intake based on Food and Drug Administration (FDA) recommendation [89]. For many diabetic patients, the most challenging part of the nutrition therapy is self-adaptation / control and following a food plan. So, it is important for those patients to be guided by a knowledgeable and skilled dietitian [90].

The restriction in calorie intake can be achieved either indirectly by self-adaptation or directly by surgical procedures as bariatric surgery. This surgery is initiated as a treatment of morbid obesity. Currently it is an effective method in both the prevention and control of DM. The most common types of surgeries used are laparoscopic Roux-en-Y gastric bypass (RYGB), and laparoscopic sleeve gastrectomy [91]. According to Arterburn, et al., [92] these surgical procedures were classified into mal-absorptive procedures, and restrictive procedures, in which the stomach’s capacity became smaller, or a combination of both types with a goal of modifying the stomach and intestines to reduce food intake and change how the body absorbs food for energy to treat obesity and control DM. Metabolic surgery has proved to provide long-term and substantial weight loss, remission of obesity-related disorders, improved quality of life, and longer life expectancy.

Weight gain and obesity's metabolic comorbidities (e.g., type 2 diabetes) were identified early in the pandemic as risk factors for COVID-19 infection. An analysis of a large prospective cohort study showed a linear association between body mass index, severe COVID-19 and admission to the intensive care unit. According to Aminian et al [93] patients with obesity who underwent metabolic surgery achieved substantial weight loss, which was associated with improved outcomes of infection with COVID-19. Moreover, according to this large, retrospectively matched cohort comparing patients who underwent weight loss surgery with propensity score matching non-surgical patients, both groups experienced the same rates of positive SARS-CoV-2 tests [94]. Therefore, it was concluded that metabolic surgery was also linked to lower hospitalization rates, oxygen requirements, and severe COVID-19 infection.

Uncertainties and hesitancies about the role of vaccination in decreasing the challenges faced by DM patients:

The main goal of diabetes management is to normalize insulin activity and blood glucose levels to reduce the development of acute and chronic complications. Therefore, in order to reduce the problems of diabetes, treatment strategies usually include insulin therapy or oral hypoglycemic agents as well as lifestyle changes such as increased physical activities and dietary interventions [10]. In addition, vaccinations should be given to all diabetic patients to break the cycle of infection. As the COVID-19 pandemic began to evolve as well as its treatment

strategies, another challenge was reported among DM patients, which is the uncertainties and hesitancies regarding the immunization against COVID- 19.

Immunization hesitancy refers to a delay in accepting or refusing a vaccine, even when it is readily available [95]. In numerous published studies [8 &9], hesitancy or refusal to accept vaccines has been reported [96 &97]. There is a correlation between perceived risks, inadequate knowledge, and religious beliefs that cause vaccine refusals. Additionally, recent data suggests that people are hesitant about the COVID-19 vaccination. There is a strong correlation between vaccination intentions and perceived safety, according to one study [99]. There is another study that concludes religious beliefs may reduce the intention to get the COVID-19 vaccine [100] A study conducted in the UK found that distrust of the vaccine and fear of adverse effects in the future played a major role in achieving mass immunity against COVID-19, where unwillingness to get vaccinated was common among the general population [101].

Nearly four million deaths have been reported worldwide since the start of this pandemic. Vaccines and protective measures are the best weapons against this deadly disease since there is no diagnosis or a cure. In turn, this will reduce hospital and intensive care admissions [102]. Currently, four types of vaccines are available against COVID-19, namely inactivated or weakened virus vaccines, protein-based vaccines, viral vector vaccines, and RNA/DNA vaccines [103]. For COVID-19 vaccination to be successful, it will be necessary to achieve sufficient vaccine coverage and a high vaccination acceptance rate. Most governments, however, face the problem of vaccine hesitancy as the most pressing issue. Studies throughout the world have shown that citizens distrust health authorities, governments, healthcare workers, and a lot of misinformation has spread through the social media [104]. Vaccine hesitancy was listed as one of ten major threats to global health by the World Health Organization (WHO) [100]. Russian, Jordanian, Kuwaiti, European, and African countries had the lowest vaccination acceptance rates for COVID-19 among adults. Meanwhile, Ecuadoreans, Malaysians, Chinese, and Indonesians were reported with the highest levels [105].

Considering the limited supply of the vaccine for the time being, the priority assignment of groups is paramount after the availability of COVID-19 vaccination. In regards to DM, individuals with diabetes who are younger have a higher mortality risk compared to those who are older. Additional factors contributing to COVID-19 risk include high BMI, diabetes duration, glycemic control, comorbidities, and the type of diabetes. Group-level prioritization is essential at this critical time, and this is what most governments have initiated so far [106].

Even though the Saudi government took proactive measures to curtail the spread of the disease right from the start of the pandemic, such measures are insufficient on their own. Several national studies found that uncertainty over vaccines and the general population's reluctance present a significant challenge to creating herd immunity through universal coverage [107]. Hence, while planning a vaccination program, it is crucial to consider Saudi Arabia's vaccine willingness since its healthcare system is publicly funded and Corona-virus-related diagnostic and treatment services are available to all residents of the Kingdom

free of charge. In a recent cross-sectional study conducted by Aldossari et al [108] in Saudi Arabia, with a total number of 709 diabetic patients, concluded that the relatively fast production process, lack of trials and uncertainties regarding the genetic components of the vaccine account for most of the uncertainties about vaccinations, despite the fact that 44.6% of the total participants, received information about COVID-19 and its vaccination via TV, social media, and ministry websites.

VII. How will diabetes and COVID- 19 be treated in the future?

It is expected that all kinds of revolutionary technologies compete for market share on the global diabetes drugs market by 2026, which is predicted to reach billions of costs. In addition to microchips that can detect type 1 diabetes before symptoms show, Nano robots that carry glucose sensors and deliver insulin, and silica particles that can slow digestion and reduce diabetes and obesity. Scientists have already proposed that these technologies could become a reality soon. No matter what the future brings, millions of lives will be affected. Regarding COVID-19 and its variants, in addition to vaccination, all hospitals have developed protocols to treat patients with diabetes and COVID-19. These examples include changing protocols on diabetic ketoacidosis management, using non-insulin agents in ICUs and non-ICUs, and implementing continuous glucose monitoring [109-112].
Figure 2 is adopted from (Pasquel, and Umpierrez(2020), (Palermo, Sadhu AR, McDonnell (2020); (Zhou, Al-Jaghbeer, and Lansang (2020);and (Raymanet al.,(2020)

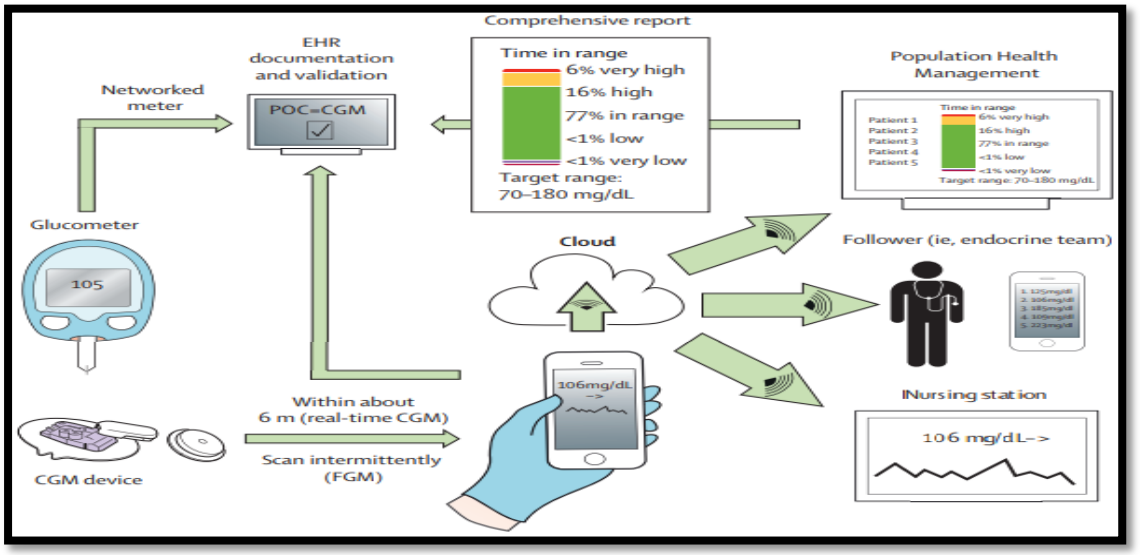

Figure 2 shows that with the COVID-19 pandemic, real-time glucose monitoring is possible utilizing a CGM or flash glucose sensor that transmits data via Bluetooth. Its data can be transferred from a smartphone to the cloud (via cellular signal or Wi-Fi) and distributed in real time (to medical providers and telemetry

systems) as well as to dashboard software (e.g., Libre View or Dexcom CLARITY) for comprehensive assessment across multiple patients. The glucose chart can be customized by scanning and uploading comprehensive glucose reports. As long as more data are not available regarding the reliability of inpatient CGM, hybrid approaches are recommended. For blood glucose concentrations >100 mg/dL, data can be documented and validated in an EHR (e.g., sensor values are within 20% of POC glucose values).
Recently, Galindo and colleagues 18 detailed the steps for the implementation of CGM during COVID-19, and Espinoza and colleagues137 described the steps for directly integrating CGM data into EHRs. Additional information, scientific literature, and links can be found online.

*Abbreviations: CGM stands for continuous glucose monitoring. Electronic health records are known as EHRs. FGM=flash glucose monitor. POC stand for Point-of-care

Conclusion and Recommendations

- Diabetes and SARS-CoV-2 infection worsen each other, and diabetics are more likely to develop severe COVID-19. This infection is also associated with newly diagnosed diabetes. The SARS-CoV2 virus is extremely contagious and can be transmitted via respiratory droplets from infected individuals. Comorbidities such as cardiovascular disease and hypertension have also been associated with severe cases of COVID-19.
- Many studies have linked DM with various kinds of infections, proving that it is a vital risk factor. The dysregulation of immune response experienced by diabetics plays a significant role in exacerbating the severity. In addition, diabetic patients may be more susceptible to COVID-19 infection due to chronic conditions such as obesity, cardiovascular disease, and hypertension, as well as altered expression of ACE2.
- It is likely that public awareness and opinion will influence the amount of protection methods and ultimately the results of clinical research. In turn, it is essential to study the characteristics of COVID-19 in diabetic patients and treat other comorbidities along with COVID-19 infection, especially among elderly patients who already have serious and critical infections.
- In addition, because of the inter-relationship between psychopathological symptoms of psychiatric disorders and diabetes (and vice versa), it is necessary to screen every patient suffering from a mental disorder for diabetes (and vice versa). Several studies have shown that diabetes mellitus, depression, and schizophrenia have significant associations. This indicates the necessity of screening patients for these conditions and referring patients for psychosocial support and mental health care.
- Therefore, it is advised that when evaluating a patient for depression, one of the effective and simple option is to ask if there is a persistent depressed mood before the formal mood questionnaire is administered.
- The treatment of psychiatric disorders with antipsychotic drugs like olanzapine, clozapine, risperidone, and some others have been linked to metabolic syndrome. To confirm an early diagnosis and ensure optimal glycemic control, it is advised that patients taking such medications should be monitored on a regular basis. Perhaps it is more appropriate to

use ziprasidone and sertindole in individuals at a high risk of developing diabetes.

- More work is needed to be directed toward the development of community health professionals' specialists, who are qualified to address emotional distress and identifying the basic aspect of mental health interventions
- The fact that observational studies in this field are limited indicates that psychiatrists and allied professionals have responded highly and multidimensionally to the COVID-19 pandemic and they realized that mental health of people specially diagnosed with chronic diseases such as diabetes, respiratory and heart disease must be taken seriously on multiple levels by health professionals.
- Another limitation reported that the number of patients affected by this pandemic continues to grow, especially in Asian and African countries, who are not just facing challenges of not only do you deal with many identified obstacles and limitations, but also have to deal with opportunities of applying many research studies including diabetics patients with psychological disorders. as a result, their challenges and problems will be solved and managed in the future [52].
- In conclusion, all scientific evidence clearly emphasizes that the medical community in general, and psychiatry in particular, should acquire a holistic treatment approach, aiming for the total wellbeing of the patients, including their physical, mental, and emotional dimensions.

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