

**CARDIOVASCULAR COMORBIDITY OF COVID-19 DISEASE: A REVIEW**Suruchi Singh\*<sup>1</sup>, Pankaj Bhatt<sup>2</sup>, Narjes Alfuraiji<sup>3</sup>, Mahdi M. Thuwaini<sup>4</sup> and Ali Esmail Al-Snafi<sup>5</sup><sup>1</sup>School of Pharmacy, Glocal University, Delhi-Yamunotri marg, Saharanpur, India.<sup>2</sup>Department of Pharmaceutics, KIET Groups of Institutions (KIET School of Pharmacy), Muradnagar, Ghaziabad, Uttar Pradesh, India.<sup>3</sup>Department of Pharmacology, College of Medicine, University of Karbala, Iraq.<sup>4</sup>College of Medical and Healthy Techniques, Southern Technical University- Basrah.<sup>5</sup>Department of Pharmacology, College of Medicine, University of Thi Qar, Iraq.**\*Corresponding Author: Suruchi Singh**

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**ABSTRACT**

Many studies have approved that COVID-19 disease caused by Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), and has spread in epidemic from across the world today. Initially, they affect the upper respiratory tract, induce viral infection in the lungs, and cause severe pneumonia in COVID-19 infected patients. After their infected body, they show changes in the other biomarkers in the body and imbalance the body response studied by the pathophysiology of the virus. However, this infection starts comorbidity directly and indirectly in COVID-19 infected patients. During this period of infection, the immune system is also suppressed by the virus and initiates other diseases. In the study of current work, the authors focus on the cardiovascular comorbidity of COVID-19 in the current work. In the COVID-19 comorbidity study, the virus mainly affects patients with hypertension. The risk factor of comorbidity of hypertension and cardiovascular disorder is 30.7% and 11.9% with diabetes mellitus. In this study, we reveal the pathophysiology, treatment, and management of cardiovascular diseases, their risk factor, and the medicinal results of patients infected patients. SARS-CoV-2 primarily targets ACE-2 receptors because this virus receives this receptor as a host for the cellular entry of the virus in the body; this leads to down-regulation in the maintenance of BP, and the body suffers from multiorgan failure. Other diseases related to CVS like inflammatory cardiomyopathy, congestive heart failure, irregular heartbeat, embolism events, and coronary infarction, also affect its pathophysiology.

**KEYWORDS:** SARS-COV-2, comorbidity, pharmacotherapy, ACE-II receptors, CVS complications, COVID-19.**1. INTRODUCTION**

In December 2019, a virus was seen in Wuhan City, China, which had pneumonia symptoms. However, it was disrupting the respiratory system by causing damage to the respiratory organs rapidly, after which problems such as asphyxia were coming named coronavirus. On 11 March 2019, the WHO declared it an epidemic worldwide due to the rapidly increasing cases of COVID-19. Subsequently, measures have been taken to prevent it worldwide, and due to all this, several procedures are being taken to improve patients' wellbeing. While writing this review, 30,826,897 patients have received worldwide, and more than 958,512 people have lost their lives due to the epidemic, and this figure is increasing day by day. People with high blood pressure, excessive weight, heart disease, stress, etc., are highly endangered to the COVID-19 epidemic.<sup>[1]</sup> This epidemic has caused the most damage, particularly in elderly patients.<sup>[2]</sup>

**2. COVID-19**

The WHO proclaimed COVID-19 as one of the significant health concerns worldwide. The maximum population of about 23 million people is being affected due to this virus.<sup>[3]</sup> There are two types of coronavirus: extreme acute respiratory syndrome coronavirus-1 and 2 and Middle East coronavirus syndrome. Severe acute respiratory syndrome and coronavirus of the Middle East are spreading frequently. These are the types of infections that are being transferred from creatures to each individual. In the worst cases, the coronavirus can spread to lung infections, kidney dysfunction, and even. Until now, there is no immunization to fight for coronavirus. The symptoms that show that the person is being affected are fever, less sleep, tiredness, breathing challenges, muscle hurt, and hack. The infections symptoms are shown within seven days, and yet it takes at least 14 days for symptoms to appear. People of any age can be affected by this virus.<sup>[4]</sup> It is not much severe

for 80% of the patient with COVID-19 with very little or negligible side-effects. 15% of the cases with COVID-19 are severe. In which 5% out of 15 cases are of serious concern. 98% of the individual being affected to date are very critical.<sup>[5]</sup> The individual with previous diseases like diabetes, asthma, etc. can be more affected by severe sickness for the COVID-19 virus. The patient with the disease diabetes has more chances of being affected and less chance of being cured because of the solutions of blood glucose level, leading to diabetic confusion.<sup>[6]</sup> COVID-19 spreads by air beads spread when the individual cough, sneeze, talks, or sniffs without covering the mouth. On the basis of the ecological condition, the infection can spread within a few hours or a few days. It is spread by close contact with the affected individual or through airbeds. Let it affect the mouth and nose. Therefore, cleanliness and social distancing should be followed.<sup>[7]</sup>

### 3. Diabetes Mellitus

Diabetes mellitus is a series of metabolic infections that lead to a disfigurement of insulin discharge and insulin activity, explained by continuous hyperglycemia. Regularities of metabolic's in lipids, starch, and proteins are essential like an anabolic hormone. The qualities responsible for these metabolic irregularities are the low degree of insulin, fat, tissue, signal transduction framework, skeleton muscles, etc. The variety and period of diabetes are responsible for the seriousness of its side effects. Patients with type-2 diabetes are asymptomatic in an early stretch of the condition. Stamped hyperglycemia is in the remaining diabetic patient. Polyuria, polyphagia, weight reduction, polydipsia, and Obscured vision other side effects seen in kids. Diabetes, which is not kept under control, can lead to excess tiredness, deep sleep if not treated properly. It is caused by ketoacidosis.<sup>[8-10]</sup>

#### 3.1. Classification of diabetes mellitus

The grouping of diabetes plays a vital role in suggesting treatment. In this category, only a few patients without efforts fit in solitary class, mainly the more youthful adults,<sup>[1-7]</sup> and 10% out of these are arranged in revision. American Diabetes Association ADA in the year 1997 proposed the traditional style that characterized diabetes.

- Type 1 diabetes mellitus
- Diabetes mellitus of type two
- Many more types of diabetes mellitus
- Gestational diabetes mellitus (GDM)<sup>[8]</sup>

#### 3.1.1. Diabetes Mellitus Type-1

##### 3.1.1.1. Autoimmune type-1 Diabetes Mellitus

In type 1 diabetes mellitus autoimmune, the patient has 5% to 10% type 1 diabetes mellitus.<sup>[11]</sup> This type of diabetes occurs because of irritation found in the pancreas due to  $\beta$  cells.<sup>[12,13]</sup> Type 1 diabetes is commonly seen in 80 to 90% of individuals with adolescents and younger age. The beta-cell present in the pancreas destroys the inflammatory response of T cells, reducing insulin production, and causing type 1 diabetes

mellitus type-1.<sup>[14]</sup> The formation of auto-antibodies in islet cells present inside the pancreas signifies type first diabetes mellitus, but its pathophysiology has not yet been clarified.<sup>[15]</sup> Islet autoantibodies, corrosive glutamic decarboxylase, protein tyrosine phosphate (IA2 and IA2b), Zinc carrier protein, and autoantibodies to Insulin are the elements present in autoantibodies.<sup>[16]</sup> Such pancreatic autoantibodies have the properties of type 1 diabetes, and we can identify such antibodies in human serum before one month or year and detect type-1. These type one diabetics have a strong association with HLA and possess the properties of DQ and DQ.<sup>[8]</sup> They can be positive and constructive. Insulin emission is not equal in type 1 autoantibody diabetes, and this problem is mostly seen in youth and adolescence.

##### 3.1.1.2. Idiopathic type-1 diabetes mellitus

Type-1 diabetes is a notorious type that results in a noncommunicative origin that is not more severe than the autoimmune type, and diabetes is responsible for the cause of what causes immunity. African faces this type of diabetes and result in a deficiency of Insulin and rambling ketoacidosis.<sup>[17]</sup> That is why it is expected that it is concerned with idiopathic type-1 diabetes. For five years, 40% of work is treated with Insulin, about 5 out of 21 based on oral agents, and 4 out of 33 related to Insulin have the next science in Ketoacidosis. It has been proven that greater chances do not have this type of diabetes. No information is not given on insulin and the intense part of diabetic ketoacidosis. This knowledge helps to distinguish from the patients suffering from type-1 or type-2DM.

Youth who grow from type-2 diabetes develop ketoacidosis in which ketones build up to a dangerous level in your body, making it is easy to diagnose. It is settled that youth and Youthful grown-up with diabetes mellitus and the type of diabetes are here, leads to Ketoacidosis, which is the reason for diagnosis.<sup>[18,19]</sup>

##### 3.1.1.3. Fulminant type-1 diabetes

After the early stage of Hyperglycemia, high glucose level, it is being explained by Ketoacidosis with an impossible degree of C peptide (C-peptide is a by-product of insulin formation by the pancreas) in the blood it is a pointer for the secretion of endogenous Insulin (refers to the Insulin the pancreas make).<sup>[20]</sup> Anti-viral resistance reaction removes the devastation leading to a quickening safe response with no difference in autoantibodies bodies fight pancreatic beta-cell.<sup>[11]</sup> Along with pregnancy, the Association of Fulminant Type One Diabetes.<sup>[21]</sup> has been reported.

##### 3.1.2. Diabetes Mellitus Type-2

The metabolic syndrome shown in 1988 is type-2 DM.<sup>[22]</sup> Earlier it was known by the name non-insulin subordinate DM that is being described as a type of DM shown in Hyperglycemia.<sup>[23]</sup> relative insulin deficiency and Insulin.<sup>[24]</sup> People affected by this are more unprotected against this as they face more problems that

resulted in unexpected passing. The patient with type 2 DM faces bitterness, coldness, and mortality due to regularity in these diabetes.<sup>[25]</sup>

#### 4. Possible Interaction Between Diabetes And Infection With Covid-19

Due to the viral infection, the risk factor for diabetic patients is increasing because of the septic course. It is seen in 20% of patients. The main contributor to the disease seriousness in the respiratory syndrome of the Middle East is diabetes.<sup>[26]</sup> The proofs were taken from observations by an epidemiologist in the region where SARS-Cov-2 is positively affected. Reports that appear for the disease's control and prevention show that the risk is more than half in diabetic patients.<sup>[27]</sup> There are multiple ways to explain that diabetic patient changes can lead to an increase in COVID-19. Few effects explain that diabetes causes an increase in infection in diabetic patients, such as neutrophil chemotaxis, defects in innate immunity, and cell-mediated immunity. The chances of occurrence are seen among patients with type-2 diabetes. However, diabetes associated with cardiovascular disease in older people helps explain the connection with the fatal outcome that results in COVID-19. Playing an essential part in COVID-19 infection minimum of two mechanisms is used. The first one shows the picture of the target cell that is SARS-COV-two viruses that show an endocrine pathway playing a severe part in the regulation of Blood pressure, Inflammation, and metabolism.<sup>[28]</sup> The receptors used in coronavirus spike proteins are angiotensin converting enzyme 2.

The information is considered as protective effects with ACE2. Infection helps decrease the expression of ACE2, leading to respiratory failure, cellular damage, and high inflammation.<sup>[28]</sup> Acute hyperglycemia has been shown to regulate ACE to expression for the cells that help inculcate virus entry. It stated that diabetes means not be the chance that results in COVID-19 disease and even with the person of the onset of new diabetes, and chronic Hyperglycemia is known for its down-regulation, which ACE is an expression that helps regulates the cell to the effects that damage the virus. Pancreatic  $\beta$  cells are the result of ACE2 expression. It results in  $\beta$  cell function.<sup>[29-31]</sup> However, this formula has not been proved in humans. It stated that diabetes might not be a concerning element for the only form of COVID-19 disease and the person with onset new diabetes.<sup>[29-31]</sup>

Potential B-cell damages caused due to viruses result in a deficiency in insulin that is being Supported by comments from Italian fellow workers and co-authors is recommending that a frequent case in the concerning ketoacidosis is being reported during the time of hospital admission. One more recording by the co-author is leading to variations in a variety of centers worldwide, which of a COVID-19 is the requirement of the insulin in the patient in the critical time of infection. The reason for COVID-19 is not known because of which factor

resulted in insulin resistance. After personally experiencing by Co-authors, they have given the conclusion that the increase in insulin resistance in the patients who have diabetes is very appropriate to compare with the sickness caused due to other factors. The next mechanism that can explain the connection between diabetic patients and COVID-19 is the dipeptidyl peptidase-4 enzyme being witnessed in the people facing diabetes of Type II. Studying the sale of DPP4 was known as the Functional Receptor Responsible Virus in the Erasmus Human Coronavirus Erasmus Medical Center and the reason behind MERS.<sup>[32]</sup>

DPP4 is also called functional receptors that are the reason for MERS in Erasmus human coronavirus medical centers. Transmembrane glycoprotein is referred to as DPP-4enzyme or adenosine deaminase complexing protein 2. It has a significant role in glucose metabolism that results in an increasing rate of Inflammation in type-2 diabetes.<sup>68</sup>Influence of the infection is not known whether it is applied to diabetic treatment for DPP-4 or the patients with COVID-19. These mechanisms can be translated for SARS-COV-2 with use in DPP-4 agents that help reduce the concentration and can help in the treatment of COVID-19.<sup>[33]</sup>

#### 5. Onset of Diabetes in Covid-19

A connection found between diabetes and the COVID-19 and connection is a mutual connection. From a perspective, the connection to diabetes is an extended risk of extraordinary COVID-19. Then again, the new beginning hyperglycemia and the complexity of the serious metabolic processes of the previous case of diabetes, including ketoacidosis resistant diabetes mellitus, and abnormally high osmolarity or which high doses of Insulin are particularly appropriate, seen in patients with COVID-19 patients.<sup>[34,35]</sup> Diabetes mellitus (DM) is frequently distinguished as a free danger factor for creating respiratory parcel contaminations. According to some studies, there is a relationship between glucose level in the blood and SARS (Severe acute respiratory syndrome).<sup>[31]</sup> Likewise, there are a few points of reference for the most prominent reason for ketosis-inclined diabetes, including different COVIDS.<sup>[36]</sup>

#### 6. Epidemiology of Diabetes

The probability of infection due to diabetes increases even more. According to old research, there has been a J curve relationship between people admitted to the hospital due to hb1c infection and respiratory tract infection. The spread of the H1N1 influenza virus spread, the infection was very high in this case, but nothing has been seen in the case of COVID-19.<sup>[37-39]</sup> In one investigation, the prevalence of diabetes disease in Chinese patients (1590) with COVID-19 is 8.2%, like the prevalence of diabetes disease in China. However, 34.6% is the rate of diabetes in patients with extreme COVID-19.<sup>[34]</sup> China gave a meta-analysis based on six research and detailed that the pervasiveness of diabetes in China

was like the commonness of diabetes in the entire COVID-19 companion (n=1527).<sup>[40]</sup> In Northern Italy, the prevalence of diabetes was accounted for to be 6.7% among 146 patients with COVID-19 (average age 65 years).<sup>[41]</sup> According to an observation conducted on patients who were suffering from COVID-19 in New York City, the abundance of obesity and diabetes was higher than those hospitalized ones who were not hospitalized.<sup>[42]</sup> A meta-analysis of 6 studies reported that 42 patients suffering from COVID-19 and with diabetes disorder had the risk of getting admitted to Intensive care unit (ICU) have increased.<sup>[42]</sup> According to an analysis in Italy, 31.95 patients had a pervasiveness of diabetes disease in patients (2895) dying of COVID-19.<sup>[43]</sup>

**7. Diabetes Management in Covid- 19 Patients**

The Department of Endocrinology has developed a protocol that describes people with diabetes with COVID facilities. This includes three documents:

- Clinical Guide on Screening for Hyperglycemia in Hospitalized Patients with COVID-19
- Clinical Guidance on Antihyperglycemic Treatment Initiation and Titration in Patients with COVID-19 and Diabetes
- Clinical Guide for Diabetes Management at COVID-19 Patient Management Facility

**7.1. Clinical Guidance on Screening for Hyperglycemia in Hospitalized Patients with Covid-19**

In the COVID-19 epidemic, Hyperglycemia is the primary cause of the continued decrease in health and increased mortality of hospitalized patients. An estimate states that patients with diabetes are better than those whose diabetes history is known.<sup>[44]</sup> The rules practiced by the endocrine society for hyperglycemia patients suggest that all patients with mental disorders undergo

blood glucose testing to diagnose diabetes by blood glucose (BG) tests when hospitalizing.<sup>[45]</sup>

**7.1.1. The proposed technique for investigation of Hyperglycemia in low asset settings and its basis**

It is suggested that every patient admitted to the hospital with COVID-19 contamination undergo a paired capillary glucose evaluation (before and 2 hours after meals). Instead of single irregular Blood Glucose estimation, we support paired blood glucose readings, which are determined by the fact that:

1. Biological variability is currently more prominent for the current prandial analysis on fasting blood glucose.<sup>[46]</sup> the latter, an option that relies on arbitrary BGs in the post-election situation alone, may be mistaken.
2. The value of the blood glucose level depends on taking the food; therefore, it is not right to monitor blood glucose levels to adopt a uniform threshold without correlating with food intake.

**7.1.1.1 Proposed limits for acceptance of Hyperglycemia and subsequent activity**

In patients whom blood glucose levels were found before meal (BG < 7.8 mmol/L, 140 mg/dL), and after meals (BG < 10.0 mmol/L, 180 mg/dL) respectively, may not justify further checking. Therefore, people whose blood glucose level figures are above these values, then they especially need to monitor their blood sugar for the next 24 hours(2 hours after the next meal and dinner).<sup>[47,48]</sup>

**7.2. Clinical guidance on Antihyperglycemic treatment initiation and titration in patients with COVID-19 and diabetes**

Table 1 represents the data in which we discuss the patient's condition in administering to the hospital, their blood glucose level, and the action to be taken. In this table, various drugs are also involved in treating the patient with COVID-19 and diabetes.

**Table 1: Clinical guidance on Antihyperglycemic treatment initiation and titration in patients with COVID-19 and diabetes.<sup>[1]</sup>**

Scheme	Level of blood glucose	Action to be taken
Recognized to have Hyperglycemia at admission	Less than 140mg/dl (before meal) Less than 180mg/dl (after meal)	Provide a healthy diet and do not require further observation
	The extent of blood glucose extent is more than/equal to 140mg/dl. The extent of blood glucose extent is more than/equal to 180mg/dl.	Checking blood glucose levels and diabetes diet
	In between 150 and 180mg/dl (before meal) Between 200 and 250mg/dl (after meal)	Start medication: Metformin- 500mg (Twice a day) Vildagliptin-50mg (Twice a day)
	The extent of blood glucose extent is more than/equal to 180mg/dl. The extent of blood glucose extent is more than/equal to 250mg/dl.	Insulin (Basal and Bolus)
	The extent of blood glucose extent is more than/equal to 300mg/dl.	Insulin (IV infusion)
	The extent of blood glucose extent is	Insulin (IV infusion)

	more than/equal to 400mg/dl. Diabetic ketoacidosis							
Oral antidiabetic patients on admission	Less than 140mg/dl (before meal) Less than 180mg/dl (after meal)	<table border="1"> <tr><td>Continue existing oral antidiabetic drugs</td></tr> <tr><td>Update oral antidiabetic drugs</td></tr> <tr><td>Insulin (Basal and Bolus)</td></tr> <tr><td>Basal Insulin (Bedtime)</td></tr> <tr><td>Insulin (IV infusion)</td></tr> <tr><td>Insulin (IV infusion)</td></tr> </table>	Continue existing oral antidiabetic drugs	Update oral antidiabetic drugs	Insulin (Basal and Bolus)	Basal Insulin (Bedtime)	Insulin (IV infusion)	Insulin (IV infusion)
	Continue existing oral antidiabetic drugs							
	Update oral antidiabetic drugs							
	Insulin (Basal and Bolus)							
	Basal Insulin (Bedtime)							
	Insulin (IV infusion)							
	Insulin (IV infusion)							
The extent of blood glucose extent is more than/equal to 140mg/dl. The extent of blood glucose extent is more than/equal to 180mg/dl.								
The extent of blood glucose extent is more than/equal to 180mg/dl. The extent of blood glucose extent is more than/equal to 250mg/dl.								
The fasting plasma blood glucose level is more significant than/equal to 140mg/dl.								
The extent of blood glucose extent is more than/equal to 300mg/dl. The extent of blood glucose extent is more than/equal to 400mg/dl.								
Diabetic ketoacidosis								
Restore basal bolus during ingress or follow-up	Less than 140mg/dl (before meal) Less than 180mg/dl (after meal)	<table border="1"> <tr><td>Continue the basal-bolus regimen again.</td></tr> <tr><td>Improve the dose of Insulin</td></tr> <tr><td>Insulin (IV infusion)</td></tr> <tr><td>Insulin (IV infusion)</td></tr> </table>	Continue the basal-bolus regimen again.	Improve the dose of Insulin	Insulin (IV infusion)	Insulin (IV infusion)		
	Continue the basal-bolus regimen again.							
	Improve the dose of Insulin							
	Insulin (IV infusion)							
	Insulin (IV infusion)							
The extent of blood glucose extent is more than/equal to 140mg/dl. The extent of blood glucose extent is more than/equal to 180mg/dl.								
The extent of blood glucose extent is more than/equal to 300mg/dl. The extent of blood glucose extent is more than/equal to 400mg/dl.								
Diabetic ketoacidosis								
Diabetic ketoacidosis								
Patients who cannot get anything in their mouth	More significant than/equal to 180mg/dl (2 hourly)	Insulin (IV infusion)						

**7.3. Clinical guidance on diabetes management in the COVID-19 patient management facility**

Screen each patient on confirmation for Hyperglycemia with two paired blood glucose values (1 before a meal and one value after meal) by a glucose-measuring machine called Glucometer. Every diabetic patient should start on a diabetic diet. Please ensure that the patient adheres strictly to time and volume.<sup>58</sup> On the off chance that an individual with diabetes creates manifestations of fever, hack, or difficulty breathing, it is proper to promptly contact a specialist (initial contact is by telephone, except if serious indications). Due to any doubt of potential COVID disease, the specialist may elude the patient to a nearby or appropriate approved clinic for additional examination (test for COVID-19 with confinement, etc.).<sup>[49]</sup> On the off chance that the individual is confirmed to have COVID-19, a different administration will be according to the suggested guidelines by the Indian Council for Medical Research.<sup>[47]</sup> However, in the table portraying uncommon contemplations against diabetic medications, we note that two generally used gatherings, sulfonylureas, and pioglitazone, are missing. Of these, pioglitazone, a PPAR- $\gamma$  agonist, legitimizes further discussion, since it partners with both instruments that may expect a section in patients with diabetes and COVID-19.<sup>[49]</sup> Pioglitazone

up-regulates the articulation of ACE2 in rat tissues, 3 prompting the hypothesis that its use may build vulnerability to and severity of COVID-19 because ACE2 acts as a co-receptor for extreme acute respiratory syndrome COVID 2 (SARS-CoV-2) to enter the cell.

However, in addition to up-regulation of ACE2 in insulin-touchy tissues in creatures, specifically the liver, fat tissue, and skeletal muscle, there is no proof that pioglitazone up-regulates the articulation of ACE2 in alveolar cells. Then again, as Bornstein and colleagues,<sup>[50]</sup> by expanding ACE2 articulation in insulin-touchy tissues, pioglitazone may help improve the destructive impacts of abundance angiotensin II. Moreover, utilizing homology displaying and sub-atomic docking strategies, Wu and colleagues four have demonstrated that pioglitazone is an expected inhibitor of 3-chymotrypsin-like protease is fundamental for RNA combination and replication of SARS-CoV-2. In any case, this product-based expectation of pioglitazone, which possibly inhibits the SARS-CoV-2 RNA blend and replication, needs approval in both in vitro and in-vivo considers. Pioglitazone is a cheap enemy of the diabetic drug, widely used around the world. It can do more advantage than hurt, and in our view, it can very well may be securely proceeded in people with diabetes

and COVID-19, aside from in clear conditions in which its utilization is not suggested, including indicative cardiovascular breakdown and liver brokenness with altogether raised transaminases.<sup>[51]</sup> Most COVID-19 related agreement articulations suggest halting sodium-glucose cotransporter-2 inhibitors (SGLT2i) and metformin during acute sickness and adhering to the day off principles. Glucagon-like receptor for peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP-4i), and insulin are the supported elements explicitly for hospitalized patients who are hospitalized.<sup>[52]</sup> There has been some conversation about the utilization of ACE inhibitors and angiotensin receptor blockers (ARBs) being related to more awful results in patients suffering from coronavirus, especially in those patients who have diabetes. Be that as it may, taking into account information indicating possible advantages, the current suggestion is to proceed with these treatments.<sup>[53]</sup> Currently, various examinations are trying hydroxyl chloroquine or chloroquine for the counteraction of COVID-19. Careful glucose checking will be required in patients with diabetes because these drugs pass antidiabetic properties, with the expected danger of low blood glucose level or hypoglycemia that is related to an expanded danger of heart arrhythmia, cardiovascular occasions, and mortality.<sup>[54]</sup>

### 8. Self-Management

The proof of interventions intended to advance self-administration in patients with diabetes that are possibly plausible in misfortune settings includes cell phone applications, web or PC-based interventions, text informing and self-checking of blood glucose.<sup>[55,56]</sup>

### 9. Effect on Diabetes Management

It is not known about the clinical relevance of the mechanisms mentioned above, but those who are taking care of this should be aware and informed about the implications that diabetes patients face.<sup>[57,58]</sup> It has been shown in a flowchart the risk factor that the diabetic patient with COVID-19 is facing. Patients who have diabetes, which is type-2, lead to other components such as dyslipidemia, hypertension, etc. Therefore, patients are given antihypertensive medications and lipid-reducing food along with the diet. ACE-2 inhibitors can recharge the virus that enters the cell.<sup>[59]</sup> According to the European Society of cardiology (ESC), Heart Failure Society of America (HFSA), American College of Cardiology (ACC), American Heart Association (AHA), it is being endorsed in the statement, which basically except the continuation of treatment with AT1 receptor antagonists and angiotensin-converting enzyme inhibitor.<sup>[60]</sup> Statins.<sup>[61]</sup> have been shown to restore high lipid-induced ACE2 deficiency, such as high-density lipoprotein or lipoprotein (A).<sup>[62]</sup> Usually, obesity and diabetes problems depend on innate and adaptive immunity that has the characteristic of chronic and acute inflammation with a greater concentration of unhealthy leptin and fewer anti-inflammatory adipocyte complement-related proteins.<sup>[63]</sup>

### 10. Comorbidities

It re-evaluates and examines the patients with COVID-19 the patient with COVID-19 and diabetes have the following percentage of hypertension, cardiovascular disease, and cerebrovascular disease: 56.9%, 20.9%, and 7.8% and non-diabetic patient, the percentage was found to be 28.8%, 11.1%, and 1.3%. Furthermore, patients with high blood glucose level and the patient without problems such as diabetes had a higher predominance of comorbidities, for example, hypertension, cardiovascular disease, cerebrovascular ailment,<sup>[66]</sup> interminable pneumonic disease.<sup>[67]</sup> and kidney infection, individually,<sup>[68]</sup> with a percentage of 83.9%, 45.2%, 126.1%, 12.9%., 6.5% And in those patients who did not have diabetes, their percentage was 50.0%, 14.8%, 5.7%, 3.3%., 3.3% respectively. Cox multi-relapse trials.<sup>[65]</sup> in patients with diabetes, CVS disorders, and interminable respiratory disease were found to be 1.87, 0.88-4.00, and 2.77, 0.90-8.54, respectively, which is one of the leading causes of excessive exposure in this epidemic. A survey conducted in patients who had diabetes in the COVID-19 epidemic found that out of 904 patients, 139 in whom diabetes was found were a significant cause of increased mortality.<sup>[69,70]</sup> Patients with diabetes during the COVID-19 epidemic, those more conventionally had high blood pressure, CVS disorder, actual framework ailment, and continuous renal contamination; CVS affliction, tactile framework sickness, and constant kidney illness were associated with the danger of the end and defenseless gauge.<sup>[71]</sup> In a CORONADO,<sup>[72]</sup> it has been found that timely treatment of patients who were suffering from diabetes found a glomerular filtration rate of 60 mL/min per 1.73 m<sup>2</sup> or less, which in itself indicates a good step.<sup>[73-75]</sup>

### 11. The Mortality Rate In Diabetic Subjects Infected By Covid-19

Epidemic infections have been terrifying and damaging humanity for decades. Populations have been ravaged by viruses and typhoids, poor sanitation, bacterial infections and high mortality. They both reappear intermittently, but antibiotics are typically best handled by sanitary and insect vectors. Viral epidemics are continuing, by comparison. A widespread epidemic (pandemic), which caused millions of deaths in 1918, was caused by a single influenza virus. Coronaviruses have also triggered several previous incidents of viral infections. A pandemic epidemic called the 2019 coronavirus disease is now caused by one of such extreme acute coronavirus 2 syndromes (SARS-CoV-2) (COVID-19). This new coronavirus, still infected but without symptoms, was transmitted rapidly by humans. It induces serious disease and sometimes mortality owing to lung and systemic injuries in susceptible persons. Most (87 percent) of the 44,672 patients in China with infection reported by nucleic acid analysis by mid-February were between the ages of 30 and 79 years. The overwhelming majority (81%) were found to have a mild disease, but 14% were labelled extreme and 5% crucial. 2,3 % of the patients died in all reported cases. For those aged 80 years or

over (14.8%), people with pre-existing coronary heart disease (10.5%) and males (2.8%) were found to have higher mortality rates compared to females (2.8 percent). (1.7%), respectively). For those with diabetes, the mortality rate was 7.3%, more than three times that of the general population. Two more prominent diabetes conditions were also associated with higher mortality rates: 10.5 percent for coronary heart disease and 6.0 percent for hypertension. Since mortality risks have not been stratified by era, it is not known how much the excess risk has been personally attributed to the age of these disorders for patients.<sup>[76]</sup> The second most frequent co-morbidities among 1382 patients is induced by DM (mean age 51.5 years, 798 males). In diabetic patients, there was a significant improvement in the risk of admission to the ICU (OR: 2.79, 95 percent CI 1.85-4.22,  $p < 0.0001$ ,  $I^2 = 46\%$ ). Diabetic subjects examined in 471 patients (mean age 56.6 years, 294 males) led to a greater incidence of secondary outcome mortality (OR 3.21, 95 percent CI 1.82-5.64,  $p < 0.0001$ ,  $I^2 = 16$  percent).<sup>[77]</sup>

## 12. The Prevalence Of Covid-19 Infections In Diabetic Patients Compared To Other Metabolic Pathologies

Emerging findings indicate that COVID-19 is predominant in patients with diabetes, asthma and cardiovascular disease (CVD); however, in various research and country-specific evidence, the prevalence rate differed. From 10 Chinese trials ( $n = 2209$ ), the composite findings for COVID-19 patients showed that the incidence of high blood pressure, diabetes and CVD was 21 percent, 11 percent and 7 percent, respectively. In a meta-analysis of 46,248 COVID-19 patients, in the eighth sample, COVID-19 patients recorded a 17 percent 8 percent, and 5 percent prevalence of hypertension, diabetes, and CVD. A working group of 20, 982 patients with COVID-19 at the Centre for Disease Control and Preventive Epidemiology in China has found that hypertension, diabetes, and CVD are associated with about 13 percent, 5 percent, and 4 percent of patients. In comparison to experimental diabetes, an Italian analysis by Onder *et al.* was equivalent to 36 percent, while CVD was correlated with COVID-19 in around 43 percent of 355 patients. Similarly, in a small sample of 24 US patents, 58.0 percent of COVID-19 patients were associated with diabetes. Although the analysis of the Italian COVID-19 surveillance community ( $n = 481$ ) noticed that 34 percent of COVID-19 patients were diabetic, 11% of the 7162 COVID-19 patients were identified by the COVID-19 response team of the US Disease Control and Prevention Centers (CDC).<sup>[78]</sup>

## 13. The Consequences Of The Infection By Covid-19 On Mental Health In Diabetic Subjects

The systemic and self-management of diabetes was questioned in the COVID-19 pandemic. Access to treatment and self-management are affected by the continued emotional distance and lockout. During a lockdown, increased emotional tension and shifts in

sleep behavior tend to be a chronic problem. Anxiety arose mainly from the contract of infection, was restricted to residence for a prolonged period of time and did not see loved ones. More than 80% of participants in North India reported that high levels of anxiety were reported by COVID-19, of which 12.5% mentioned sleeping problems. A further study in China found that, due to the COVID-19 pandemic, 53.8% of the participants had a mild to extreme impact on their mental well-being. Similarly, the EU member state of Malta has provided a series of guidelines to control and alleviating the fear associated with COVID-1 in the local community of diabetes. During the COVID-19 pandemic, the National Health Service (NHS) published 'GUIDANCE FOR Supports individuals with diabetes,' compiling supportive websites that the diabetic community needs to discuss in these tough days. In addition to this suggestion, a range of nations, including the European country of Malta, have created a dedicated helpline for all individuals with psychiatric disorders, including the diabetic population.

Although COVID-19 and associated stress may induce sleep disorders, nutrition, lifestyle, and diseases must also be taken into consideration. In fact, shorter sleep and erratic sleep cycles have been linked with obesity and cardiovascular problems. The association between sleep disorders and T2DM patients with higher rates of insomnia, long daytime sleep and more regular usage of sleep medicines has also been identified. Type 2 diabetes mellitus and the resulting problems such as polyuria and peripheral neuropathy may be responsible for these changes in sleep patterns.<sup>[78]</sup>

## CONCLUSION

Diabetes is an epidemic that poses an extreme risk if it is not diagnosed in the initial state. Patients with diabetes are at extreme risk for COVID-19, which requires special attention to their health. Given the number of diabetic patients around the world, they represent a very vulnerable category of COVID-19. This review highlights the type of diabetes and the dangerous effects of diabetes on humans in this epidemic. Due to lockdown, the danger in COVID-19 pandemic to the medicine available in the diabetes market, and many more chronic diseases increases. In particular, compared to those who did not have diabetes, those who had diabetes and had glycemic levels under control have shown a decrease in side effects caused by COVID-19. That is why, in this epidemic, patients affected by diabetes need to be careful and take extreme precautions to avoid its profound effects.

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**Conflict of Interest**

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**REFERENCES**

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese center for disease control and prevention: Summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA*, 2020; 323(13): 1239-1242. doi:10.1001/jama.2020.2648
2. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020; 395(10223): 470-473. doi:10.1016/S0140-6736(20)30185-9.
3. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res.*, 2020; 7(1): 4. doi:10.1186/s40779-020-0233-6
4. Chan-Yeung M, Xu RH. SARS: epidemiology. *Respirology*, 2003; 8: S9-14. doi:10.1046/j.1440-1843.2003.00518.x
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 2020; 395(10223): 497-506. doi:10.1016/S0140-6736(20)30183-5.
6. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis.*, 2020; 71(15): 732-739. doi:10.1093/cid/ciaa237.
7. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014; 37(Supplement\_1): S81-90. doi:10.2337/dc14-S081
8. Craig ME, Hattersley A, Donaghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. *Pediatr Diabetes*, 2009; 10(12): 3-12. doi:10.1111/j.1399-5448.2009.00568.x
9. Galtier F. Definition, epidemiology, risk factors. *Diabetes Metab.*, 2010; 36(6/2): 628-651. doi:10.1016/j.diabet.2010.11.014
10. Shibasaki S, Imagawa A, Hanafusa T. Fulminant type 1 diabetes mellitus: a new class of type 1 diabetes. *Adv Exp Med Biol*, 2012; 771: 20-23. doi:10.1007/978-1-4614-5441-0\_3.
11. Daneman D. Type 1 diabetes. *Lancet*, 2006; 367(9513): 847-858. doi:10.1016/s0140-6736(06)68341-4.
12. Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. *BMJ.*, 2004; 328(7442): 750-754. doi:10.1136/bmj.328.7442.750.
13. Dabelea D, Mayer-Davis EJ, Saydah S, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA.*, 2014; 311(17): 1778-1786. doi:10.1001/jama.2014.3201.
14. Vermeulen I, Weets I, Asanghanwa M, et al. Contribution of antibodies against IA-2 $\beta$  and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. *Diabetes Care*, 2011; 34(8): 1760-1765. doi:10.2337/dc10-2268.
15. Couper J, Donaghue KC. Phases of diabetes in children and adolescents. *Pediatr Diabetes*, 2009; 10(12): 13-16. doi:10.1111/j.1399-5448.2009.00574.x
16. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*, 2003; 26(1): S5-20. doi:10.2337/diacare.26.2007.s5.
17. Wilson C, Krakoff J, Gohdes D. Ketoacidosis in Apache Indians with non-insulin-dependent diabetes mellitus. *Arch Intern Med.*, 1997; 157(18): 2098-2100. doi:10.1001/archinte.157.18.2098.
18. Umpierrez GE, Casals MM, Gebhart SP, Mixon PS, Clark WS, Phillips LS. Diabetic ketoacidosis in obese African-Americans. *Diabetes*, 1995; 44(7): 790-795. doi:10.2337/diab.44.7.790
19. Imagawa A, Hanafusa T. Fulminant type 1 diabetes—an important subtype in East Asia. *Diabetes Metab Res Rev.*, 2011; 27(8): 959-964. doi:10.1002/dmrr.1236.
20. Patlak M. New weapons to combat an ancient disease: Treating diabetes. *FASEB J.*, 2002; 16(14): 1853e. doi:10.1096/fasebj.16.14.1853e.
21. Damjanov I. Robbins and cotran pathologic basis of disease, 7th edition. *Shock*, 2005; 23(5): 482-483. doi:10.1097/00024382-200505000-00016.
22. Azevedo M, Alla S. Diabetes in sub-saharan Africa: kenya, mali, mozambique, Nigeria, South Africa and zambia. *Int J Diabetes Dev Ctries*, 2008; 28(4): 101-108. doi:10.4103/0973-3930.45268.
23. Chee YJ, Ng SJH, Yeoh E. Reply to comments on Letter to the Editor - Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res Clin Pract*, 2020; 166(108305): 108305. doi:10.1016/j.diabres.2020.108305.
24. Memish ZA, Perlman S, Van Kerkhove MD, Zumla A. Middle East respiratory syndrome. *Lancet*. 2020; 395(10229): 1063-1077. doi:10.1016/S0140-6736(19)33221-0.
25. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet*. 2020; 395(10231): 1225-1228. doi:10.1016/S0140-6736(20)30627-9.
26. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven

- protease inhibitor. *Cell.*, 2020; 181(2): 271-280.e8. doi:10.1016/j.cell.2020.02.052.
27. Bindom SM, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. *Mol Cell Endocrinol.* 2009; 302(2): 193-202. doi:10.1016/j.mce.2008.09.020
28. Roca-Ho H, Riera M, Palau V, Pascual J, Soler MJ. Characterization of ACE and ACE2 expression within different organs of the NOD mouse. *Int J Mol Sci.*, 2017; 18(3): 563. doi:10.3390/ijms18030563.
29. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol.* 2010; 47(3): 193-199. doi:10.1007/s00592-009-0109-4.
30. Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature.* 2013; 495(7440): 251-254. doi:10.1038/nature12005.
31. Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? *Diabetes Res Clin Pract.* 2020; 162(108125): 108125. doi:10.1016/j.diabres.2020.108125.
32. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab.*, 2020; 22(10): 1935-1941. doi:10.1111/dom.14057.
33. Ren H, Yang Y, Wang F, et al. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. *Cardiovasc Diabetol.* 2020; 19(1): 58. doi:10.1186/s12933-020-01035-2.
34. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA.* 2003; 289(21): 2801-2809. doi:10.1001/jama.289.21.JOC30885.
35. Garbati MA, Fagbo SF, Fang VJ, et al. A comparative study of clinical presentation and risk factors for adverse outcome in patients hospitalised with acute respiratory disease due to MERS Coronavirus or other causes. *PLoS One.*, 2016; 11(11): e0165978. doi:10.1371/journal.pone.0165978.
36. Schoen K, Horvat N, Guerreiro NFC, de Castro I, de Giassi KS. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. *BMC Infect Dis.*, 2019; 19(1): 964. doi:10.1186/s12879-019-4592-0.
37. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J.*, 2020; 55(5): 2000547. doi:10.1183/13993003.00547-2020.
38. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospitalization and critical illness among 4,103 patients with Covid-19 disease in New York City. *bioRxiv.* Published online, 2020. doi:10.1101/2020.04.08.20057794.
39. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. *J Clin Virol.* 2020; 127(104354): 104354. doi:10.1016/j.jcv.2020.104354.
40. EpiCentro. Coronavirus. Iss.it. Accessed March 17, 2022. <https://www.epicentro.iss.it/coronavirus/aggiornamenti>
41. Shi Q, Zhang X, Jiang F, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: A two-center, retrospective study. *Diabetes Care.* 2020; 43(7): 1382-1391. doi:10.2337/dc20-0598.
42. Umpierrez GE. Hyperglycemia: An independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab.* 2002; 87(3): 978-982. doi:10.1210/jc.87.3.978.
43. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.*, 2012; 97(1): 16-38. doi:10.1210/jc.2011-2098.
44. Chai JH, Ma S, Heng D, et al. Impact of analytical and biological variations on classification of diabetes using fasting plasma glucose, oral glucose tolerance test and HbA1c. *Sci Rep.*, 2017; 7(1): 13721. doi:10.1038/s41598-017-14172-8.
45. Ceriello A, Stoian AP, Rizzo M. COVID-19 and diabetes management: What should be considered? *Diabetes Res Clin Pract.*, 2020; 163(108151): 108151. doi:10.1016/j.diabres.2020.108151.
46. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr.* 2020; 14(3): 211-212. doi:10.1016/j.dsx.2020.03.002.
47. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol.* 2020; 8(6): 546-550. doi:10.1016/S2213-8587(20)30152-2.
48. Wondafraash DZ, Desalegn TZ, Yimer EM, Tsige AG, Adamu BA, Zewdie KA. Potential effect of hydroxychloroquine in diabetes mellitus: A systematic review on preclinical and clinical trial studies. *J Diabetes Res.*, 2020; 2020: 5214751. doi:10.1155/2020/5214751.
49. Xu Y, Tong GYY, Lee JYC. Investigation on the association between diabetes distress and productivity among patients with uncontrolled type 2 diabetes mellitus in the primary healthcare institutions. *Prim Care Diabetes.* 2020; 14(5): 538-544. doi:10.1016/j.pcd.2020.04.004.
50. Moorthy V, Henao Restrepo AM, Preziosi MP, Swaminathan S. Data sharing for novel coronavirus (COVID-19). *Bull World Health Organ.* 2020; 98(3): 150. doi:10.2471/BLT.20.251561.
51. Farsalinos K, Angelopoulou A, Alexandris N, Poulas K. COVID-19 and the nicotinic cholinergic system. *Eur Respir J.*, 2020; 56(1): 2001589. doi:10.1183/13993003.01589-2020
52. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical

- illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ.*, 2020; 369: 1966. doi:10.1136/bmj.m1966
53. Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab.*, 2020; 31(6): 1068-1077.e3. doi:10.1016/j.cmet.2020.04.021
54. Chen Y, Yang D, Cheng B, et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. *Diabetes Care*, 2020; 43(7): 1399-1407. doi:10.2337/dc20-0660.
55. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*, 2020; 109(5): 531-538. doi:10.1007/s00392-020-01626-9.
56. Zou Q, Zheng S, Wang X, et al. Influenza A-associated severe pneumonia in hospitalized patients: Risk factors and NAI treatments. *Int J Infect Dis.*, 2020; 92: 208-213. doi:10.1016/j.ijid.2020.01.017.
57. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia*, 2020; 63(8): 1500-1515. doi:10.1007/s00125-020-05180-x.
58. Aldossari KK. Diabetes mellitus is an important predictor for hospitalization and mortality from the COVID-19 infection: A substantial interface between two outbreaks. *J Endocrinol Metab*, 2020; 10(3-4): 74-78. doi:10.14740/jem665.
59. Diabetesincontrol.com. Accessed March 18, 2022. <http://www.diabetesincontrol.com/blood-glucose-control-affects-morbidity-and-mortality-in-COVID-19/>
60. Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med.*, 2006; 23(6): 623-628. doi:10.1111/j.1464-5491.2006.01861.x
61. Shimizu I, Makino H, Imagawa A, et al. Clinical and immunogenetic characteristics of fulminant type 1 diabetes associated with pregnancy. *J Clin Endocrinol Metab.*, 2006; 91(2): 471-476. doi:10.1210/jc.2005-1943.
62. Cakan N, Kizilbash S, Kamat D. Changing spectrum of diabetes mellitus in children: challenges with initial classification. *Clin Pediatr (Phila)*, 2012; 51(10): 939-944. doi:10.1177/0009922812441666.
63. Riddle MC, Buse JB, Franks PW, et al. COVID-19 in people with diabetes: Urgently needed lessons from early reports. *Diabetes Care*. 2020; 43(7): 1378-1381. doi:10.2337/dci20-0024.
64. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. *Diabetes Metab Syndr*. 2020; 14(4): 303-310. doi:10.1016/j.dsx.2020.04.004.
65. Sciberras J, Camilleri LM, Cuschieri S. The burden of type 2 diabetes pre-and during the COVID-19 pandemic - a review. *J Diabetes Metab Disord*, 2020; 19(2): 1-9. doi:10.1007/s40200-020-00656-4.