Diabetes and the COVID-19 Pandemic, What should diabetes patients know about COVID-19?

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Cases of respiratory disease have been caused by the outbreak of the novel coronavirus named COVID-19: "CO" for corona, "VI" for virus, and "D" for disease. The "19" represents 2019, the year the infection started in Wuhan City, China, since when it has since spread worldwide.

COVID-19 ranges in severity from a mild, flu-like disease through pneumonia and respiratory failure to death. Severe symptoms, complications, and a high risk of infection are associated with elderly patients, along with chronic diseases like diabetes, as reported in a recent study [1, 2].

Rapidly accumulating evidence suggests patients are more likely to be male and have a comorbidity such as hypertension, diabetes, cardiovascular disease, or chronic lung disease. One study has shown that old age, cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer are all associated with an increased risk of death [3,4].

The huge number of over 2 million cases of COVID-19 had been recorded by 18 April 2020, and this figure has continued to increase on a daily basis. In 2019, it was estimated that 9.3% of the global population had diabetes, a percentage which is expected to rise continuously over the next few years [5]. Approximately 2.4% of the patients who died from COVID-19 had chronic diseases like diabetes [6]. Studies carried out in China, Italy, Spain, and Romania of

COVID-19 and comorbidities found that diabetes is the second most common comorbidity in fatal cases after hypertension [7,8]. Recent evidence showed that diabetic patients are at higher risk of hospitalization and mortality than other patients. When we compare intensive care unit (ICU) and non-ICU COVID-19 patients, the ICU cohort is twice as likely to have diabetes as the non-ICU cohort. Moreover, mortality is three times higher for COVID-19 patients with diabetes than other COVID-19 patients [9,10].

There is a lack of recent studies showing the link between diabetes and COVID-19-related mortality. However, one study has established that coronaviruses (SARS-COV and SARS-COV 2) bind to the cell via the angiotensin-converting enzyme 2 (ACE2), which is expressed in the epithelial cells of the kidney, blood vessels, lung, and intestine. The appearance of ACE2 is markedly increased in diabetic patients (type-1 and type-2 patients) who are taking ACE inhibitors and angiotensin II type-I receptor blockers (ARBs) for their condition. Hence, taking these two drugs will increase ACE2, which will in turn facilitate infection by COVID-19 [11,12].

In 2006 a study showed the relation between plasma glucose levels and mortality in diabetic patients with SARS, which belongs to the same family as COVID-19. It found that diabetic patients, especially type-2, usually have excess adipose tissue, which increases the chronic inflammatory and prooxidative states which have a negative effect on glycemic values. Therefore, it affects glycemic homeostasis and insulin sensitivity [13]. Consequently, chronic hyperglycemia and inflammation statuses are responsible for the immunosuppression in type-2 diabetic patients that increases the risk of COVID-19 infection and mortality.

Other mechanisms that may increase the risk of COVID-19 infection in diabetic patients include elevation in plasmin levels, imbalance in cytokines, increased inflammatory markers, reduced viral clearance, and insulin resistance [14]. However, these hypotheses have not yet been tested and more observational studies are needed.

Very few studies have addressed the question of whether diabetic patients are at higher risk of COVID-19 infection. Of those that have been carried out, one concluded that diabetic patients are not at higher risk of catching the novel coronavirus, but, once infected, will develop severe symptoms that could lead to ICU admission or death [15]. Another study found that diabetes may increase the development of the COVID-19 infection [16]. It may be that the risk of being affected by coronavirus is the same across non-diabetic and diabetic patients. However, the severity of the symptoms varies from one patient to another depending on the risk factors. It is

important to monitor risk factors to know which are most likely to decrease symptoms, mortality, and morbidity. These risk factors include:

1- Glucose level in the blood. Good glycemic control is among the major factors that affect the severity of the illness. Hence, the patient should control their glucose level during infection to decrease the chances of superadded bacterial pneumonia. Moreover, constant hyperglycemia will damage the blood vessels in the human body, and therefore the circulatory system. Blood has a healing effect as it is sent to reach the site of infection, but damage to the blood vessels will prevent this effect from taking place [16, 18].

2- Adequate nutrition intake. Any vitamin or mineral deficiencies will affect the patient's condition. For example, it has been stated that Vitamin D deficiency increases the tendency to systemic infections, damages immune response, and increases the development of autoimmune disorders [19].

3- Taking SGLT2 inhibitor therapy to monitor glucose levels. These drugs may cause diabetic ketoacidosis (DKA). Viral infection also increases the risk of DKA, and affects the fluid and electrolyte level in the body, which has an effect on the patient's condition. It is therefore better to change to a different oral hypoglycemic medication or insulin. If patients do continue with SGLT2 inhibitor therapy, they should use ketone test strips to monitor their ketone level and manage their fluid and electrolyte intake [15].

4- Age group. Diabetic patients over 65 have a higher risk of morbidity and mortality than those under 65. However, severity of symptoms is not affected by age [20].

5- Presence of other chronic diseases, such as diabetes, hypertension, or renal, cardiovascular, or chronic lung disease (asthma and COPD). These patients will be at higher risk of hospitalization and severe symptoms. They should be made aware that monitoring these diseases is very important to control infection [21].

6- Smoking and obesity. Both these are risk factors for diabetic and non-diabetic patients, but more dangerous for the former group. As regards smoking, there are not yet enough data to prove this but as concerns obesity, data suggest that this will increase insulin resistance, which in turn leads to an increase in the viral replication in the host resulting in increasing severity of symptoms [22].

7- Low immunity. Diabetic patients mainly have low immunity (immunosuppressed) due to the high glucose level which causes dysfunction in their immune system. People with

low immunity are more susceptible to complications when they become infected with COVID-19 [23].

8- Coagulation factors. Diabetic patients are most likely to have an imbalance between fibrinolysis and clotting factors. This leads to an increased risk of thromboembolic events. However, studies have found that COVID-19 increases coagulation activity due to dysfunction in the endothelial, which is associated with hypoxia. Hence, the intra vessels in this case are more favorable for coagulation during infection. Diabetic patients diagnosed with COVID-19 have a higher concentration of D-dimer and longer prothrombin time [24].

Diabetic patients with COVID-19 need especial clinical care and attention and should adhere to government instructions to protect themselves and their families. Certain guidelines must be followed by patients with diabetes and COVID-19, drawn up by scientific societies such as the International Diabetes Federation. These include the following precautions to avoid becoming infected with the virus.

- Patients and their families should stay at home, and leave only in cases of emergency.

- They should keep to their medical regime during quarantine. Monitoring their glucose level is very important to prevent hypoglycemic events.

- It is essential they continue to take their medicines and monitor not only hyperglycemia but other metabolic syndrome like hypertension.

- If the patient is taking ACEI, the doctor should change the treatment, as it leads to increased ACE 2, which eases the entry of the virus into the vessels. The doctor should prescribe a different oral hypoglycemia, such as metformin or dipeptidyl peptidase-4 inhibitor (DDP4), or patients can use insulin [25]. One study showed that DDP4 has an important role in metabolic and immune diseases and so is commonly used in type-2 diabetic patients [26].

- A healthy diet is an essential factor in diabetes management. Eating a varied and balanced diet will keep blood sugar levels stable and enhance immunity. Recommended foods are those with a low glycemic index: fruits, vegetables, and lean proteins like fish, eggs, milk, and meat. Patients should avoid fried food and limit their intake of food containing carbohydrates and fat.

- Physical activity will be beneficial for patients as it increases their immunity and controls their glucose level.

- If a patient wants to fast, they must ask their doctor and should be aware of the possible risks and what to do if these eventuate. For example, one of the most important risks is that there could be a decrease or increase in glucose level, so the patient should monitor their blood glucose level regularly and break their fast if they notice any symptoms of hyperglycaemia, hypoglycaemia, or dehydration. If people with diabetes develop any symptoms of COVID- 19 during fasting, the fast must be promptly broken [27].

- Remote glucose monitoring or self-glucose monitoring offers a novel means of infection control for diabetic patients and will minimize the risk of passing COVID-19 infection from nurses to patients or vice versa [28].

- Finally, if patients have symptoms of a flu-like syndrome, they should immediately contact their health care providers [29,30].

It is particularly important that diabetic patients are advised to constantly observe good hygiene practices to avoid infection. The International Diabetes Federation recommends the following steps to diabetic patients.

1- Wash your hands regularly with soap.
2- Avoid touching your face before washing your hands.
3- Clean and sterilize any surface which has been touched frequently.
4- When coughing and sneezing, cover your mouth and nose with a tissue or your arms.
5- Try to avoid contact with anyone suspected of being infected or who has the symptoms of flu.
6- Do not share any personal items or items such as glasses, food, or towels [31].

Possible treatment for diabetic patients infected with COVID-19.

There is very little evidence about how to manage COVID-19 infection in diabetic patients. The use of drugs should be minimized because of their side effects on diabetic patients. For example, hydroxychloroquine could cause hypoglycemia and must be used with caution if the patient is using insulin; lopinavir/ritonavir may cause hyperglycemia and can interact with statins (potentially increasing the risk of hepatic and muscle toxicity); and glucocorticoids cause hyperglycemia and increase susceptibility to secondary bacterial infection. Treatment should be restricted to patients with virologically confirmed COVID-19 [32].

In conclusion, the symptoms of COVID-19 in diabetic patients are more likely to be more intense due to many risk factors (immunity, obesity, SGLT2 inhibitors drugs, etc.). This is a new infection, data are lacking, and vaccines are still under development. To minimize the possibility of infection, these patients should follow their physician's instructions and the guidelines referenced above. More studies are needed to have a full picture of this disease, and how to treat, avoid, and deal with it.

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