Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 and diabetes: The why, the what and the how

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ABSTRACT

Background: The novel coronavirus SARS-CoV-2 has taken the world by storm. Alongside COVID-19, diabetes is a long-standing global epidemic. The diabetes population has been reported to suffer adverse outcomes if infected by COVID-19. The aim was to summarise information and resources available on diabetes and COVID-19, highlighting special measures that individuals with diabetes need to follow.
Methods: A search using keywords "COVID-19" and "Diabetes" was performed using different sources, including PubMed and World Health Organization.
Results: COVID-19 may enhance complications in individuals with diabetes through an imbalance in angiotension-converting enzyme 2 (ACE2) activation pathways leading to an inflammatory response. ACE2 imbalance in the pancreas causes acute β-cell dysfunction and a resultant hyperglycemic state. These individuals may be prone to worsened COVID-19 complications including vasculopathy, coagulopathy as well as psychological stress. Apart from general preventive measures, remaining hydrated, monitoring blood glucose regularly and monitoring ketone bodies in urine if on insulin is essential. All this while concurrently maintaining physical activity and a healthy diet. Different supporting entities are being set up to help this population.
Conclusion: COVID-19 is a top priority. It is important to remember that a substantial proportion of the world's population is affected by other co-morbidities such as diabetes. These require special attention during this pandemic to avoid adding on to the burden of countries' healthcare systems.

1. Introduction

The causative virus SARS-CoV2, also known as COVID-19 or Coronavirus has taken the world by storm as it spread from China to 215 countries, areas and territories over weeks.[1,2] As of 12th May 2020, there have been a total of 4,013,728 reported infected cases worldwide with 278,993 deaths.[2] Another long-standing global epidemic is diabetes that was reported to affect 463 million adults (20–79 years) in 2019, which accounts for 9.3% of the world's population in this age group.[3] The global health expenditure in 2019 for this chronic disease was estimated to be 760 billion dollars and resulted in an estimated 4.2 million deaths during the same year.[3] Individuals with diabetes have been identified to have worse outcomes when infected by COVID-19.[2,4,5] In fact, individuals with diabetes who get infected with COVID-19 were reported to have higher non-survival prevalence (ranging between 22 and 31%) compared to the non-diabetes subgroup.[6] The global focus has been to control the pandemic outbreak while trying to protect the general population. Individuals with diabetes have been declared as being a vulnerable group. The aim of this review is to provide a comprehensive summary of the emerging information (up till time of writing) on individuals with diabetes and COVID-19, why individuals with diabetes are considered as vulnerable and what measures have been recommended for this population to date.

2. Methods

A literature search using "COVID-19" and "Diabetes" as the keywords was performed through PubMed and Google. Published articles pertaining to the aim of this review were considered. Furthermore, the search was extended to international organizations websites in order to establish recommendations and information published by these entities for the diabetes population. The international organizations included were: World Health Organization (WHO), American Diabetes Association (ADA), International Diabetes Federation (IDF) and Centres for Disease Control and Prevention (CDC).

3. Why is the diabetes population at risk?

Studies originating from China have reported that individuals with diabetes and infected by COVID-19 showed higher admission rates to hospitals, development of severe pneumonia as well as higher mortality rates, when compared to those without comorbidities.[7–9] As part of the pathophysiology of diabetes, especially those with an uncontrolled

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glycaemic status, the innate immune system and humoral immunity are compromised.[10] This makes the first line defence against any infection, including SARS-CoV-2 inefficient. Diabetes also causes a pro-inflammatory state with an exaggerated cytokine response. It has been reported that individuals with diabetes infected by COVID-19 had significantly increased levels of interleukin-6 (IL-6) and C-reactive protein (CRP) compared to those without diabetes.[11] The entry of SARS-CoV-2 within the host cell triggers an inflammatory response, recruitment of T helper cells with the production of interferon gamma leading to a cytokine storm.[6] Hence, considering the cellular mechanisms triggered by COVID-19 and the pathophysiology of diabetes, individuals with diabetes are more susceptible to a cytokine storm with potential organ damage if infected by COVID-19.

It is already well documented that the population with diabetes is at higher risk of community acquired pneumonia that requires admission to hospital, especially for those with an uncontrolled glycaemic status.[12–14] This corresponds to the diabetes pathological mechanism where the hyperglycaemic state of the individual increases the virulence of the pathogens, lowers the interleukins production in response to infection as well as reduces the phagocytic activity and polymorphonuclear leukocytes.[15] Type 1 diabetes individuals are at high risk of developing diabetic ketoacidosis (DKA) when acquiring an infection, which causes additional metabolic complications in these individuals. It has also been reported that the hyperglycaemic levels will directly increase the concentration of glucose within the airway secretion.[16] This is apart from the fact that diabetes is associated with pulmonary structural changes.[17]

Individuals with diabetes have reduced angiotensin-converting enzyme 2 (ACE2) expression. This is an enzyme found in multiple organs including the lungs, pancreas, kidneys, vascular system and intestinal endothelium. In normal physiology, ACE2 plays an important role in anti-inflammation and anti-oxidation. It is responsible for the degradation of angiotensin-II as well as angiotensin I (to a lesser extent) to smaller peptides, namely angiotensin (1–7) and angiotensin 1–9 respectively. The former peptide (angiotensin 1–7) is responsible for the anti-inflammatory and antioxidant role. This process is compromised as part of the diabetes pathophysiology. This makes individuals with diabetes at increased risk of severe lung injury as well as acute respiratory distress syndrome (ARDS) if infected by COVID-19.[18] COVID-19 has envelope with spike glycoprotein that helps the virus to enter human cells (through angiotension-converting enzyme 2 – ACE2) as well as is responsible for host-to-host transmission.[19] Hence, it was postulated that in severe COVID-19 infections there may be an imbalance in the ACE2 activation pathways with an increase in the pro-inflammatory response as a consequence of increase in angiotensin II levels and a decrease in angiotensin 1–7 levels.[20,21]

One needs to note that the ACE2 is also expressed in the pancreas. So, the entry of the coronavirus into the pancreatic islets may cause an acute beta-cell dysfunction with a resultant acute hyperglycaemic state.[22] Hence, individuals with diabetes are vulnerable to COVID-19 infection leading to an uncontrolled hyperglycaemic status. In fact, it was reported that in-patients with diabetes and infected by COVID-19 in Wuhan medical centre, had uncontrolled hyperglycaemic states even when following the recommended blood glucose management strategies by the American Association of Clinical Endocrinologists and American Diabetes Associations. Such uncontrolled glucose levels predispose these individuals with diabetes and infected with COVID-19 to secondary infections as well as increase in mortality risks.[23] Although a number of potential limitations in Wuhan healthcare system were noted by the authors, they suggested that the blood glucose management strategies for COVID-19 positive patients with diabetes should be optimized.[24] Such experience along with the pathophysiology of COVID-19 in individuals with diabetes is of significant clinical importance to caring physicians. This suggests that it is mandatory that patients with diabetes and COVID-19 should have optimal metabolic control. It has been suggested that the antidiabetic GLP1 agonists medication that acts on the ACE2 and Mas receptor pathways may not only help control the blood glucose levels but also prevent coronavirus from entering the cells due to competitive binding to ACE2.[25]

3.1. Diabetes management and COVID-19

The top priority for every individual with diabetes is to control the glucose level. As noted already, COVID-19 may have a role in the dysregulation of the glycaemic control. These individuals are therefore more prone to require hospitalisation for insulin management in order to control their glucose levels. Intravenous insulin infusions require frequent blood glucose monitoring by the medical staff. Consequently there is an increased exposure of healthcare workers to the COVID-19 positive individual.[6] Furthermore, in the presence of respiratory distress these individuals will also require mechanical ventilation which further increases the risk of aerosolisation of the viral particles.

Metformin is the first-line treatment option of type 2 diabetes. It is responsible for the activation of the AMP-activated protein kinase (AMPK) in the liver.[26] Historically, metformin was initially produced as an anti-influenza drug and its well-known glucose lowering ability was actually a side effect.[27] It has been postulated that metformin may have an advantageous role in this pandemic. The activation of AMPK by metformin leads to phosphorylation of ACE2 which can lead to functional changes to this receptor.[28] Such changes may decrease the binding of SARS-CoV-2. It has been reported that if the virus enters into the host cells through ACE2, it creates an imbalance of the renin-angiotensin-aldosterone system with downregulation of ACE2 receptors. However, metformin prevents this detrimental sequence by activation of ACE2 through the AMPK-signalling pathway.[29] Therefore, one can postulate that there is no contraindication for the intake of metformin if an individual with diabetes gets infected by COVID-19. On the contrary it might be beneficial to these individuals during this pandemic.

Glucagon-Like-Peptide-1 receptor agonists (GLP-1Ra), Sodium-Glucose-Transporter-2 (SGT-2) inhibitors and Dipeptidyl Peptidase 4 (DPP4) are all anti-diabetic drugs used for controlling glucose levels. The GLP-1Ra and SGLT-2 inhibitors have additional roles in the prevention of kidney and cardiovascular disease. Such roles have an additional benefit during this pandemic, where it is reported that individuals suffering from any of the aforementioned diseases have a worse prognosis if infected by COVID-19.[30] Additionally, GLP-1Ra also has anti-inflammatory and anti-adipogenic effects with insulin resistance antagonism.[31] However, considering that both GLP-1Ra and SGLT-2 inhibitors may induce ACE2 receptor over-expression,[32] these drugs may have more serious consequences if individuals with diabetes acquire COVID-19. More data and clinical studies are required to ascertain such a relationship. Of note, in those not infected by COVID-19 but on SGLT-2 inhibitors, an increased risk of diabetes ketoacidosis (DKA) has been observed. This will further complicate the clinical scenario should they acquire the virus.[33] Similarly, individuals with type 1 diabetes on SGLT2 inhibitors and infected by COVID-19 have been observed to experience severe DKA.[34] It has been recommended that individuals with diabetes infected by COVID-19 should have their SGLT2 inhibitors discontinued as a precaution against potential acute metabolic decompensation.[34]

DPP4 is currently used to treat type 2 diabetes by targeting the incretin system. Recently, it was hypothesized that individuals on DPP4 may demonstrate a reduction in the severity of SARS-CoV-2.[35] Yet, this is based on preclinical data and so caution must be exerted while waiting for clinical data on the matter.

Thiazolidinediones (TZDs) are a class of medication used in type 2 diabetes as they have a role in treating insulin resistance.[36] Additionally, pioglitazone (a TZD drug) has been reported to inhibit pro-inflammatory cytokines including IL-6 secretion.[37] Considering that a pro-inflammatory state has been associated with COVID-19 and a worse prognosis present in those with metabolic disorders (diabetes, cardiovascular disease, hypertension, metabolic syndrome), it was

hypothesized that the administration of pioglitazone may be a supporting therapy for COVID-19.[38]

ACE inhibitors (ACEi) and angiotensin-receptor blockers (ARB) are common anti-hypertensive and reno-protective drugs prescribed to individuals with diabetes. These are associated with an increased ACE2 expression with a counteractive response to the elevated levels of angiotensin-II. The ARBs have pleiotropic effects beyond controlling hypertension. They have anti-inflammatory effects, reduce endothelial injury and organ fibrosis, maintain insulin sensitivity as well as energy metabolism. Additionally, ARBs have a protective effect on lipid metabolism and normalise the coagulation cascade.[39,40] It has also been reported that ARBs protect the lungs from severe endothelial injury associated with pneumonia, influenza and sepsis.[41] During this pandemic there have been reports that individuals with diabetes on ACE inhibitors (ACEi) are at an increased susceptibility to COVID-19.[18,42] It has been postulated that when SARS-CoV-2 uses ACE2 as a host receptor, the ACE2 gets downregulated and compromises its protection to the lung tissue from injury.[18] However, there is lack of robust data and evidence on this malice relationship. In fact, the Council on Hypertension of the European Society of Cardiology, along with a consortium between the American Heart Association, the Heart Failure Society of America and the American College of Cardiology, all recommended that physicians should continue the treatment and any medication changes should only be done after careful assessment. This is especially so, when considering that ARBs have a number of protective effects.[43–45] It has been noted that those infected with COVID-19 had hypokalaemia, which has been linked with the downregulation effect of ACE2 within the lungs.[18] This causes a reduction in angiotensin-II degradation with a consequential increased secretion of aldosterone. The presence of hypokalaemia can worsen the glycaemic control in both individuals with type 1 and type 2 diabetes mellitus.[46]

Corticosteroids play a part in the treatment of ARDS and sepsis, which is one of the management plans for severe COVID-19 infection. Nevertheless, it is known that corticosteroids worsen the glycaemic control in individuals with diabetes.[47] Another medication used as a potential COVID-19 treatment is the type 1 interferons, which is known to be associated with beta cell damage. Hence, worsening the glycaemic control in diabetes.[48,49] Therefore, physicians prescribing such medications to individuals with diabetes need to keep in mind the possibility of associated uncontrolled glucose levels.

4. COVID-19 and diabetes associated co-morbidities

Obesity is a common co-morbidity affecting individuals with diabetes. Adiposity affects both the adaptive and the innate immune system with the development of chronic systemic inflammation and presence of elevated IL-6 and CRP levels.[50] Considering that both diabetes and obesity are triggers to a cytokine storm, the presence of COVID-19 infection would have a worse inflammatory effect on individuals with diabetes and obesity. This cytokine response also has an effect on insulin resistance which in turn worsens the glycaemic status.[51]

Obesity has also been linked with coagulopathy and thrombosis.[52] Similarly, COVID-19 infection was linked with thrombotic mechanisms and coagulation disturbances.[53] Additionally, individuals with diabetes and infected with COVID-19 had a higher D-dimer levels than those without diabetes.[11] Therefore, the presence of both diabetes and obesity would have a worse prognostic outcome if infected by SARS-CoV-2, with potential thrombotic events such as strokes.

The potential downregulation effect of ACE2 by SARS-CoV-2 can promote the elevation of blood pressure through vasoconstriction and activation of aldosterone. Considering that hypertension is a common co-morbidity of type 2 diabetes, infection by COVOD-19 may lead to dysregulation of blood pressure with increased susceptibility to cardiovascular complications.

Post-mortem lung histology of COVID-19 infected patients showed the presence of micro-and macro-thromboses. Vasculopathic lesions were also reported outside the respiratory system. In fact, children infected with COVID-19 were observed to have distal finger lesions similar to Kawasaki disease.[54] On the other hand, it is known that vasculopathy, both micro and macrovascular are pathophysiological complications of diabetes.[55] Hence, it can be postulated that individuals with diabetes may have a worse vasculopathic outcome if infected by SARS-CoV-2.

Individuals with diabetes are prone to psychological distress, anxiety and depression. Diabetes distress is associated with a worse metabolic profile including higher glycated haemoglobin, higher body mass index, higher diastolic blood pressure and low-density cholesterol (LDL-C). These can contribute towards diabetes related complications. This is also associated with poorer diet quality and low social support.[56,57] With the COVID-19 pandemic and the implemented lockdown, the population with diabetes is more prone to worsening of the diabetes distress. The COVID-19 stressful period may decrease the quality of life of the individuals with diabetes as well as affect the glucose self-management.[58] Hence, additional psychological aid and support is of utmost importance during this pandemic.

5. What should the individual with diabetes do?

Public health officials across the globe have been advocating a number of preventive measures aimed to protect the population as well as the vulnerable groups (including diabetes). The measures are “social distancing, staying at home whenever possible, regular hand washing with soap and water for at least 20 seconds or use alcohol-based wipes/rubs, avoid none essential travel, limit the amount of time in supermarkets”. However, it is important to advocate further measures that are specific to the diabetes population to avoid this vulnerable population from developing unwanted complications. This ensures safeguarding the demands on the healthcare system, especially at this time of crisis. It is important to note that although lockdowns and advocacy to stay at home are an essential part of COVID-19 pandemic containment measures, these may have negative consequences on individuals with diabetes. This will curtail the regular diabetes clinic consultations, will limit sunlight exposure, affect the maintenance of physical activity as well as alter the dietary habit.

5.1. Diabetes specific recommendations

Individuals with diabetes need to follow the general preventive measures however other specific measures are recommended. It is well known that hypovitaminosis D is a risk factor for insulin resistance.[59] Vitamin D supplements should be recommended to all those suffering from diabetes in order to help maintain their glycaemic control.

It is important that individuals with diabetes keep hydrated, monitor their blood glucose regularly and if on insulin, to monitor the ketone bodies in the urine. Patients with type 2 diabetes who are on oral hypoglycaemic agents and have controlled glycaemic levels should monitor their glucose levels in fasting and post-prandial states once or twice a week. If uncontrolled glycaemic levels are present, then self-monitoring should be done more frequently. Individuals with type 1 diabetes with uncontrolled glycaemic levels should check their glucose levels at least four times a day (fasting, before lunch, before dinner and at bedtime). If the glucose levels remain uncontrolled it is paramount that they seek medical aid. If glucose strips are running low, online pharmacy stores have been set up to aid in this current pandemic situation.

Regular physical activity should be encouraged especially for those individuals with diabetes.[4] Many governments have now restricted movement of their citizens and confined them to the home environment, hence public physical activity facilities have been closed. However, a number of different organizations and entities have set up online physical activity video routines that could be followed at home.

Some countries are also broadcasting a daily exercise routine for their viewers to follow. Individuals with diabetes are recommended to follow such exercise programmes however the exercise intensity should be tailored to the individual's capacity to exercise. Another important factor is for individuals with diabetes to adhere to a regular well-balanced diet. A healthy diet should consist of protein, fiber, vitamins and limited saturated fats. In this time of lockdown, acquiring fresh fruit and vegetables may be a challenge however there are companies that are delivering such fresh foods directly to residents' homes. Unfortunately, during this stressful time of the pandemic, an individual may opt for inappropriate stress eating habits, with a tendency towards packed high fat, sugar and salt content foods. Such food along with lack of physical activity is the recipe for dysregulation of the blood glucose levels, hyperosmolar coma, ketoacidosis, predisposition to infections as well as acute cardiac events in individuals with diabetes.[6] A number of doctors have set up telemedicine as an exchange for their normal consultation practices. Through the means of telemedicine, individuals with diabetes can remain in constant contact with their physician for treatment advise and management of their glucose levels.[34]

The International Diabetes Federation (IDF) recommends that individuals with diabetes should have adequate stock of medication and supplies of blood glucose monitoring apparatus at their home in order to prevent the need of leaving their house should they become sick. If diabetic individuals do fall sick, they might notice that their glycaemic control starts to deteriorate. In which case, it is essential for the individual to contact their family physician or any other healthcare helpline but not personally visit the clinic or hospital.[4]

6. How can we help the diabetes population?

Relatives, friends and neighbours of individuals with diabetes have been encouraged by public health officials to help this vulnerable population in their shopping or medication. Different countries have set in place different directorates to deal with this COVID-19 pandemic. Recently, a group of diabetes clinicians from the UK have set up a Twitter® account to help diabetes patients deal with concerns and fears related to COVID-19.[60] Similarly, NGOs such as the MAPHM – Malta Association of Public Health Medicine have set up a social media Facebook® account to bring forward verified advice from public health officials for the population including vulnerable groups as well as promote positive health behaviours.[61] There are physicians and other healthcare professions, like psychologists, that are practicing telemedicine and consultations for their patients in order to ensure their health and wellbeing are in check. Individuals with diabetes should be made well aware of these services and advised to contact their caring physician if they feel sick or if they have any questions. Diabetes educators may also advocate how individuals with diabetes can access online stores to purchase anti-diabetic medications amid the lockdown.

7. Conclusion

The COVID-19 pandemic is far from over and it is a daily struggle for all the countries to contain this crisis. It is however important to remember that a substantial proportion of the world is affected by other comorbidities such as diabetes. This vulnerable population is at an increased risk of complications should they acquire COVID-19. Hence, specific attention should be given to these individuals during this pandemic to avoid adding on more complications and burden to the healthcare systems.

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