



Indian Journal of Biochemistry & Biophysics
Vol. 57, October 2020, pp. 512-520



Minireview

Diabetes in the time of COVID-19 pandemic: A knife with two sharp ends

Shatabdi Ghosh^{*1,2}, Sanjit Dey¹ & Sujoy Ghosh³

¹Department of Physiology, UCSTA, University of Calcutta, Kolkata-700 009, West Bengal, India

²Department of Physiology, Vidyasagar College, University of Calcutta, Kolkata-700 006, West Bengal, India

³Department of Endocrinology and Metabolism, IPGME&R and SSKM hospital, Kolkata-700 020, West Bengal, India

Received 19 August 2020; revised 15 September 2020

Interactions of current pandemic COVID-19 and pre-existing major health burden Diabetes Mellitus have posed a serious global public health crisis. The emergence of COVID-19 as a communicable viral infection along with the presence of non-communicable diabetes, have transformed the health system into a knife with two sharp ends. Though diabetes worldwide is almost 20 times more than COVID-19 positive cases, the severe virulence and pathogenesis coincides with the routine treatment and pathogenesis of diabetes making it one of the most serious comorbid factors. The first three deaths due to COVID-19 reported in China were diabetes patients. The severity of the association of diabetes with COVID-19 ranges from 5 to 20%. Type 1 diabetes mellitus and type 2 diabetes mellitus increase the susceptibility to infections and their complications. The present study was attempted to review probable interaction between these two global health burdens and possible suggestive management to control their detrimental effect. An intensive online search was conducted using two databases, PubMed and Google Scholar. Most hypothesized pathways for COVID-19 infection are the ACE2 receptors and RAAS system followed by the DPP4 receptor pathway. This review proposes that proper and timely management of the COVID-19 patients with diabetes comorbidity might reduce COVID-19 disease burden.

Keywords: Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, ACE2 receptors, DPP4 receptors, RAAS system, SARS-CoV-2

Introduction

‘Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity’ as defined by the World Health Organisation (WHO) is at present facing a global crisis¹. The global impact of the novel coronavirus which is well known as COVID-19 has led to 20 million confirmed cases and a death toll of 0.6 million as reported till 15th August 2020 (WHO)². Thus it has rightly been declared as a pandemic by WHO because COVID-19 has paralysed not only the global health system but also the economic system and affected health in all aspects of physical, mental and social well-being. There are triple burdens of diseases namely 1) Communicable, 2) Non-communicable and 3) Emerging infectious. Among the non-communicable diseases (NCDs), cardiovascular diseases account for most NCD deaths (17.9 million people annually), followed by cancers (9.0 million), respiratory diseases (3.9 million), and diabetes (1.6 million)³. Almost over 80% of all premature NCD deaths are reported annually due to these four diseases.³

The global prevalence of diabetes mainly type 2 diabetes is 463 million adults (20-79 years).⁴ The prevalence of diabetes has been steadily increasing for the past 3 decades and most rapidly in low- and middle-income countries and the count is expected to cross 700 million by 2045⁴. The advent of COVID-19 as a communicable emerging infection along with the presence of non-communicable diabetes, have transformed the health system into a knife with two sharp ends. The high global prevalence of diabetes makes it a potential comorbid factor in patients with COVID-19 associated disease. Several effects especially the impaired immune response, heightened inflammatory response and hypercoagulable state have contributed to the disease severity^{5,6}. It has been observed that the severe cases of COVID-19 can rapidly progress to Acute Respiratory Distress Syndrome (ARDS), septic shock and multiple organ dysfunction syndrome (MODS)^{7,8}. The association of diabetes with COVID-19 was first reported in Chinese studies and the severity ranged from 5 to 20%⁹. Evidences relating to the impact of COVID-19 in people with preexisting diabetes is limited but continuing to emerge¹⁰. There is a bidirectional relationship between COVID-19 and diabetes. On one hand diabetes is

*Correspondence:

E-mail: shatabdi6@gmail.com

associated with an increased risk of severe COVID-19. On the other hand, new onset diabetes and severe metabolic complications of preexisting diabetes, including diabetic ketoacidosis and hyperosmolarity for which exceptionally high doses of insulin are warranted, have been reported in patients with COVID-19¹¹. Although the overall mortality rate of COVID-19 is low as 1.4 to 2.3% with certain countries, ethnicities demonstrating lower death rates but patients with comorbidities are more likely to have severe disease symptoms and subsequent higher mortality⁷. Both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) increase the susceptibility to infections and their complications¹². Viral infections have been widely associated with T1DM pathogenesis which is an autoimmune disease characterized by progressive pancreatic β -cells destruction and insulin deficiency¹³. T2DM or the adult diabetes is among the leading causes of kidney failure along with other along with other issues like cardiovascular problems, retinopathy and neuropathy making it one of the most common comorbidity of COVID-19¹⁴.

The COVID-19 pandemic is far from being solely a medical phenomenon. It has greatly impacted personal and professional lives. To contain the rapid transmission of the disease, precautionary steps like isolation, social distancing and lockdown have been imposed by the government; have significant effect on the health and lifestyle of an individual. Management of chronic diseases such as diabetes which requires dietary modification, regular exercise, good adherence to medications and routine medical assistance poses many complex challenges¹². Therefore the present study attempted to review studies related to the relation of the two global pandemics – Diabetes and COVID-19 and possible suggestive management to control the detrimental effect of them at large¹⁵.

Methodology

Search strategy

An intensive online search was conducted using two databases, PubMed and Google Scholar. “Diabetes”, “COVID-19” and “Sars-CoV-2” keywords were mainly used for the search with the interposition of the Boolean Operator “AND”. COVID-19 AND Diabetes, Diabetes AND Sars-CoV-2, were used in PubMed and Google Scholar to retrieve relevant articles. Published articles were accounted for through the period of March 2020 to August 2020. Furthermore, the renowned international organizations were also included in the search, to

establish the current information pertaining to diabetes population and coronavirus transmission. The international organizations were: World Health Organization (WHO) and International Diabetes Federation (IDF).

Inclusion criteria

Full-length scientific research articles, letters to the editor, commentaries and review articles like systematic reviews, meta-analysis and mini reviews in the English language have been included. Research articles on Randomized Controlled Trials (RCTs) on both sexes (male and female) were considered to get clear view of the hypothetical pathophysiology of COVID-19 infection. Studies showing patients of any age group suffering from COVID-19 infection with or without diabetes mellitus as the only comorbid factor were considered.

Diabetes mellitus and coronavirus

The Diabetes Mellitus (DM) represents a group of diseases of heterogeneous etiology, mostly characterized by chronic hyperglycemia and other metabolic abnormalities¹⁶. Type 2 diabetes or T2DM occurs when the body becomes resistant to insulin or doesn't make enough insulin and is one of the serious devastating diseases found in enormous proportions¹⁷. Type 1 diabetes or T1DM is characterized by auto-immune destruction of insulin-producing pancreatic β -cells and systemic derangements. A steady rise in the incidence of T1DM is happening globally¹⁸. In December 2019, an unknown respiratory infection which was fatal in certain cases was reported from Wuhan, China. Later a new virus of the coronavirus family was identified¹⁹. On 11th March WHO declared it as a pandemic²⁰. According to the World Health Organisation (WHO) some of the lethal coronavirus varieties, found to affect global public health are SARS-CoV (Severe Acute Respiratory Syndrome coronavirus) in 2002; MERS-CoV (Middle East Respiratory Syndrome coronavirus) in 2012 and the newly emerged novel coronavirus also known as SARS-CoV-2 in 2019, which was renamed as COVID-19 in 2020^{2,19}. Coronavirus is made up of four structural proteins: spike (S), membrane (M), nucleocapsid (N), and envelope (E) proteins. Like other coronaviruses, SARS-CoV-2 or COVID-19 particles are spherical and have proteins called spikes protruding from their surface^{21,22}. The S protein mediates receptor binding on the host cell membrane through the receptor-binding domain (RBD) in the S1 domain and membrane fusion through the S2 subunit²². The structure of the outer

covering made of proteins and polypeptides are easily digestible by alcohol based products^{23,24}. Although the disease supposedly originated from a zoonotic virus transmission by live wild animals, it became a person-to-person transmitted infection: the virus is mostly carried by asymptomatic or mild symptomatic people¹³. COVID-19 and diabetes represent two devastating pandemics with very different characteristics in terms of healthcare burden mainly because of different presentation (acute *vs* chronic) and transmission (communicable *vs* noncommunicable), but which may be much closer than previously thought²⁵ (Fig. 1 & 2).

Prevalence of diabetes mellitus and COVID-19

According to WHO, the global impact of the novel coronavirus which is well known as Sars-Cov-2 or novel coronavirus has led to 20966523 confirmed cases and a death toll of 608998 as reported till 15th August 2020². Whereas, the global prevalence of diabetes is 463 million adults (20-79 years) and almost 1.1 million children and adolescents with total 4.2 million deaths according to the International Diabetes Federation (IDF)⁴. The following graphical representation (Fig. 3) shows the worldwide spread of the novel coronavirus disease and its comparison with the global prevalence of diabetes (T2DM mainly). The following table represents the global COVID-19 cases and deaths in comparison with global diabetes cases and deaths due to diabetes (Table 1).

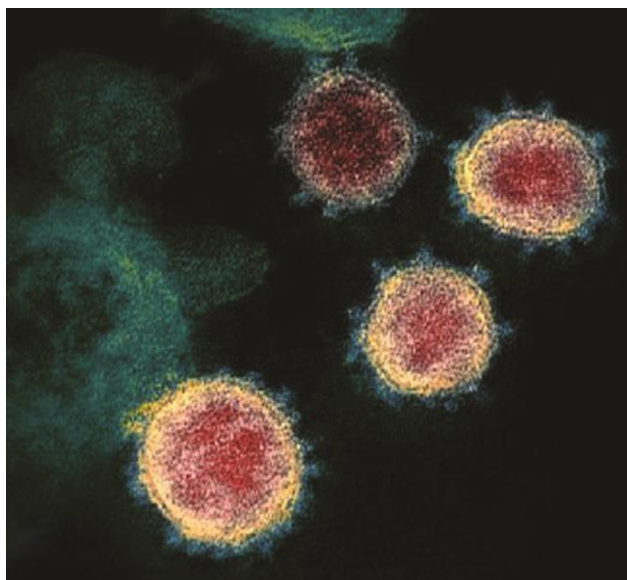


Fig. 1 — Transmission electron microscope image shows SARS-CoV-2, the virus that causes COVID-19, isolated from a patient in the U.S. Virus particles are emerging from the surface of cells cultured in the lab. The spikes on the outer edge of the virus particles give coronaviruses their name, crown like. NIAID-RML²¹

Pathogenesis of COVID-19

Various mechanisms have been suggested for probable entry and cause of infection of COVID-19 in human cells. Most pathways are detrimental to diabetics as it can aggravate the infection causing higher susceptibility and mortality rate. Figure 4 shows the graphical representation of various hypothesis given in literature that supports the pathogenesis of COVID-19. It is seen that the most supported mechanism of infection of COVID-19 is through the Angiotensin Converting Enzyme 2 (ACE2) receptor. More clinical evidence and research is warranted to validate this pathway of infection. It may be hypothesized that the aerosolized uptake of SARS-CoV-2 or COVID-19 virus invasion into the respiratory epithelium and other target cells involves its binding to cell surface angiotensin converting enzyme 2 (ACE2) receptors. Increased expression of ACE2 may favor more efficient cell binding and entry into cells. Early recruitment and function of neutrophils and macrophages are impaired in Diabetes Mellitus (DM). Delay in the initiation of adaptive immunity and dysregulation of the cytokine response in DM may lead to the initiation of cytokine storm²².

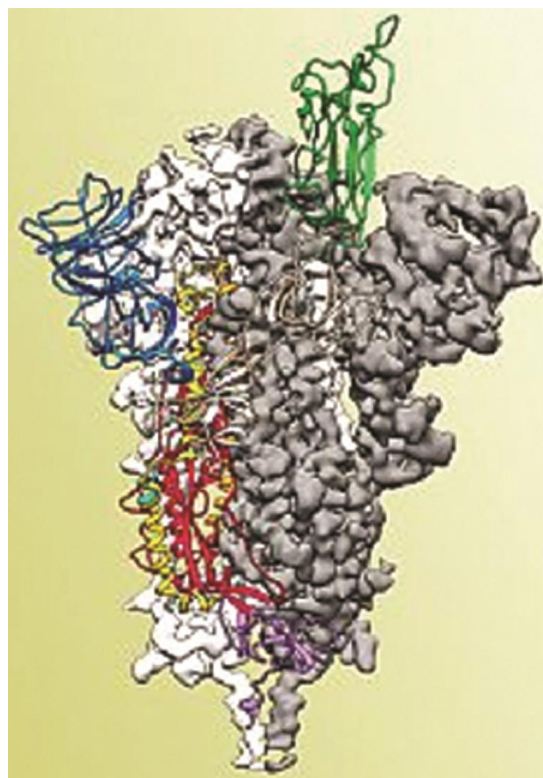


Fig. 2 — Atomic-level structure of the SARS-CoV-2 spike protein. The receptor binding domain, the part of the spike that binds to the host cell, is colored green. UT Austin, McLellan Lab²¹

Discussion

In empirical hospital based studies it has been found that around 20% of diabetics suffering from a virus are at risk of developing severe pneumonia²⁶. Epidemiological observations from regions heavily affected by COVID-19 along with reports from the Centers for Disease Control and Prevention (CDC) and other national health centres and hospitals showed that the risk of a fatal outcome from this virus is up to 50% higher in patients with diabetes than in those who do not have diabetes²⁶.

In the literature it can be seen that there are various preferable pathways that contribute to the entry of COVID-19 virus into the human cells and infect them. The most widely accepted theory is the use of Angiotensin Converting Enzyme 2 (ACE2) receptors for entry into the cells. ACE2 is a type 1 integral membrane glycoprotein that is constitutively expressed by the epithelial cells of the key metabolic organs and tissues, including pancreatic beta cells, adipose tissue, small intestine, kidneys, lungs, and blood vessels^{5,7,11}. 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^{7,27}. The former peptide (angiotensin 1–7) is responsible for the anti-inflammatory and antioxidant role. This process is compromised as part of the diabetes pathophysiology²⁷. ACE2 expression is reduced in patients with DM possibly due to glycosylation; this might explain the increased predisposition to severe lung injury and ARDS with COVID-19⁷. The expression of ACE2 is substantially increased in patients with T1DM or T2DM by medication²⁸. The ACE2 receptor may be increased using specific medications, like Glucagon like peptide-1 (GLP-1) agonists, thiazolidinediones, ACE inhibitors (ACEi), statins, and angiotensin-II type-1 receptor blockers (ARBs), all of which are frequently given to individuals with diabetes²⁹. Diabetes treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19²⁸. Insulin is the preferred agent for control of hyperglycemia in hospitalized sick patients³⁰. As an adaptive response to counteract the elevated levels of angiotensin-II, expression of ACE2 is increased. First, to gain entry to its target cells, the novel coronavirus hijacks an endocrine pathway that plays a crucial role in regulation of blood pressure, metabolism, and inflammation. ACE2 receptors on the host pneumocytes (lung cells) are used by the spike proteins for entry. ACE2 upregulation facilitates the entry and subsequent proliferation of the coronavirus³¹. ACE2 has protective effects primarily regarding inflammation. COVID-19 infection reduces ACE2 expression inducing cellular damage, hyper inflammation, and respiratory failure²⁶. Once the virus

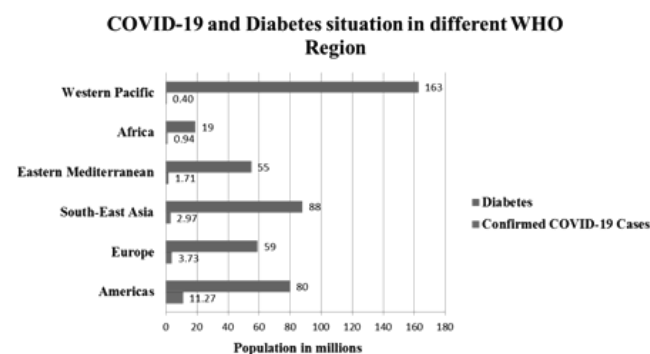


Fig. 3 — COVID-19 and Diabetes situation in different WHO region

Table 1 — COVID-19 and Diabetes situation by country

Country	COVID-19 Cases-cumulative total	COVID-19 related Deaths-cumulative total	Adults with Diabetes (20-79 years)	Diabetes related death (20-79 years)
India	2526192	49036	77005600	1010262
China	89695	4708	116446900	823780
Russian Federation	917884	15617	8288500	110530
Japan	53577	1085	7390500	71513
France	198876	30275	3480000	18656
Spain	342813	28617	3619100	15394
Italy	252809	35234	3669400	15656
UK	316371	41357	2680500	13951
USA	5203206	165995	30987900	188969
Brazil	3224876	105463	16780800	135197
Australia	22743	375	1288300	5175
New Zealand	1258	22	259800	1069

Probable mechanism of COVID-19 infection

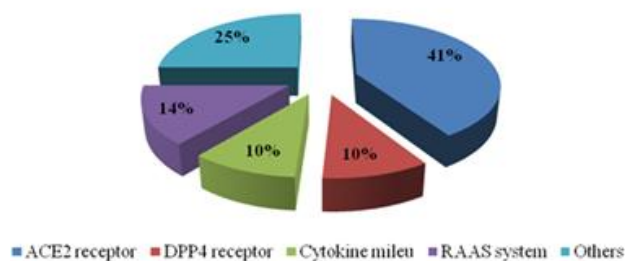


Fig. 4 — Probable mechanism of COVID-19 pathogenesis

uses the enzyme to gain entry into the host tissue, ACE2 gets downregulated and it is unable to protect against lung injury³⁰. Early coronavirus family *i.e.* SARS-CoV bind to ACE2 in pancreatic islet cells, damage them and cause acute hyperglycemia, possibly contributing to an excessive mortality rate, even among people without diabetes, similar mechanism is observed in COVID-19 too¹².

A second potential mechanism that might explain the link between COVID-19 and diabetes involves the dipeptidyl peptidase-4 (DPP-4) enzyme, which is commonly targeted pharmacologically in people with type 2 diabetes. In cell studies, DPP-4 was identified as a functional receptor for human coronavirus-Erasmus Medical Center (hCoV-EMC), the virus responsible for MERS. Antibodies directed against DPP-4 inhibited hCoV-EMC infection of primary cells. DPP-4 enzyme is a ubiquitously expressed type II transmembrane glycoprotein. It plays a major role in glucose and insulin metabolism but also increases inflammation in T2DM²⁶. Similar evidence of risk among persons with diabetes has been reported for the two earlier coronavirus infections, severe acute respiratory syndrome (SARS) beginning in 2002 and affecting more than 8000 persons, mainly in Asia and the Middle East known as Middle East Respiratory Syndrome (MERS) in 2012 affecting more than 2000 persons, mainly in Saudi Arabia. As MERS-CoV binds to the receptor-binding domain of human dipeptidyl peptidase IV (DPP-IV), a transgenic mouse model expressing this DPP-IV receptor on pulmonary alveolar cells has been used to study the effect of diabetes in worsening disease severity, showing an association of diabetes with greater weight loss and greater pulmonary inflammation, with infiltration of macrophages³². So novel coronavirus maybe assumed to follow this pathway as well.

People with diabetes are more susceptible to an inflammatory cytokine storm eventually leading to ARDS, shock and rapid deterioration due to COVID-19³¹. Interleukin-6 (IL-6), which is already increased in conditions of chronic inflammation, may play a more deleterious role in COVID-19 infection²⁵. IL-6 is a pleiotropic cytokine that mainly participates in acute phase inflammatory responses, but is seen to significantly increase in conditions of chronic inflammation such as metabolic disorders and cardiovascular diseases²⁵. Targeting the over expression of IL-6 effects with a monoclonal antibody against IL-6 receptor or using Janus Kinase inhibitors may be particularly helpful for treatment of COVID-19 pneumonia in diabetics²⁵. Interleukin-6, amongst the different markers of inflammation (fibrinogen, C-reactive protein, D-dimer) that were found to be more elevated in COVID-19 cases with diabetes than in those without, deserves particular attention²⁵. In a study it was found that, serum levels of inflammation-related biomarkers IL-6, C-reactive protein, serum ferritin and coagulation index, D-dimer, were significantly higher ($P < 0.01$) in diabetic patients compared with those without, suggesting that patients with diabetes are more susceptible to an inflammatory storm eventually leading to rapid deterioration due to COVID-19³³. Even mild COVID-19 can induce a pro-inflammatory milieu, as evident by high amounts of IL-6, IL-1 β , tumor-necrosis factor α (TNF- α), monocyte chemoattractant protein-1 (MCP-1) and inducible protein-10 that can further lead to lowering of insulin sensitivity³¹. COVID-19 patients with DM had higher D-dimer levels than those without DM; perhaps signifying over-activation of the hemostatic system. Amid an already underlying pro-thrombotic hypercoagulable state predisposed by the mere presence of DM, over-activation of the coagulation cascade in COVID-19 can lead to fatal thrombo-embolic complications and eventual mortality³¹. Non-structural proteins of SARS-CoV-2 attacks the β -1 chain of hemoglobin leading to dissociation of iron from porphyrin, thereby impairing the ability of hemoglobin to carry oxygen. COVID-19 virus may have a higher affinity to bind to glycated hemoglobin than non-glycated hemoglobin, thus making it more prone to diabetics as their glycated hemoglobin levels are higher than normal (>42 mmol/mol)³¹.

For patients with type 1 diabetes, monitoring of ketone levels (particularly for people who are persistently hyperglycaemic) and vigilance for the development of symptoms of Diabetic Ketoacidosis (DKA) are important. DKA occurs as a result of insulin deficiency

and increased counter regulatory responses, which favour the production of ketones. For type 1 diabetics with COVID-19 and hyperglycaemia, it is important to monitor their blood glucose and ketone levels also maintain hydration and continue insulin therapy¹². The interactions between COVID-19 and the renin angiotensin-aldosterone system (RAAS) might provide another mechanism in the pathophysiology of DKA³⁴. In addition, the relationship between COVID-19 and the RAAS can complicate DKA management. Excessive fluid resuscitation may potentiate ARDS as angiotensin-II increases pulmonary vascular permeability and worsens damage to lung parenchyma. Furthermore, angiotensin-II stimulates aldosterone secretion, potentiating the risk of hypokalemia, which may necessitate more potassium supplementation in order to continue intravenous insulin to suppress ketogenesis³⁴. Hypokalemia, in turn, can worsen glucose control in patients with T1DM and T2DM³¹. Thus, educating and making T1DM patients aware of this complication and about typical symptoms, if possible home-measurement of urine or blood ketones, acute behavioral guidelines, and timely professional medical advice is crucial, although it might be difficult in low and middle income countries²⁶. Frequent changes in dosage and correctional bolus may be required to maintain normoglycemia³⁰. Early reports indicate that among patients with pre-existing diabetes, DKA may be a common complication of severe COVID-19 and a poor prognostic sign³⁵.

It is not just diabetes that is making COVID-19 more deadly; it is also possible that COVID-19 is making diabetes worse²⁹. It is plausible that SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that could complicate the pathophysiology of preexisting diabetes or lead to new mechanisms of the disease¹¹. Pancreatic damage from the virus and resultant impairment in β -cell, insulin secretion could worsen preexisting diabetes or even predispose to new cases of diabetes in non-diabetic subjects. This could make hyperglycemia worse in the short term and thus lead to a more severe COVID-19 disease course triggering the emergence of increased rates of autoimmune diabetes, whereby the body coordinates an immune response to the damaged pancreas, with physiology akin to type 1 diabetes²⁹.

Neutrophil dysfunction, reduced T cell response and disordered humoral immunity are contributory, and bacterial and viral respiratory tract infections are particularly common phenomena¹². Preexisting diabetes

is significantly associated with greater risk of severe or critical illness and in-hospital mortality in patients admitted to hospital with COVID-19 infection³⁹. The histological and pathological changes in the pancreatic β -cells also pose a risk of developing new type of diabetes after COVID-19 virus infection.

Based on the evidences obtained from clinical studies and literature, it is evident that COVID-19 virus infection and its pathophysiology coincides with diabetes pathogenesis. So timely management, proper dissemination of facts and knowledge along with the adoption of variation in treatment strategy based on severity of COVID-19 infection and duration of diabetes is necessary.

Antioxidants and vitamins are hypothesized to play a protective role in COVID-19 infection and also prevent virus infection. Vitamin C supplementation has some role in prevention of pneumonia and its effect on COVID-19 needs further research and validation³⁰. Vitamin D deficiency can lead to worsening of glucose profile in patients subsequently getting infected with COVID-19³¹.

Recent management strategies adopted

Management of patients with diabetes in times of restrictions on mobility poses some challenges and novel approaches like telehealth or telemedicine or telesensitization can be useful⁵. Alternative approaches to manage people with diabetes with greater urgency and efficiency is the need of the hour. Patients with new-onset type 1 diabetes represent one of the more challenging health conditions. In a study by Garg *et al.* (2020) two case reports were presented of an adult patient (20 years old) and a child (12 months of age) where telemedicine was effectively used during COVID-19 pandemic at Colorado, USA³⁶. This case study helped to provide perspectives regarding the future applications of tele-diabetes³⁶. Hopefully, telehealth and digital diabetes care will better enable health-care providers to reach the millions of people with either type 1 or type 2 diabetes who currently do not achieve the desired level of glycemic control, thereby improving quality of care and reducing societal health-care costs³⁶. Due to the ever-increasing global prevalence and cost of diabetes associated with inadequate availability of healthcare providers and access to care, especially in remote places and in emerging economies, the majority of the patients worldwide will require adequate investments in digital health. New diabetes technologies have the promise of

Table 2 — Telemedicine support for diabetes patients by few countries during COVID-19 pandemic

Country	China	France	Italy	UK
Society	Chinese Geriatric Endocrine Society	Federation of Diabetology	Italian Society of Diabetes (SID)/Association of Italian Diabetologists (AMD)/Italian Society of Endocrinology (SIE)/ Italian Society of Pediatric Endocrinology (SIEDP)	National Charity Diabetes UK
Mode of support	Baidu Health and WeChat app	COVIDIAB (web app)	Facebook page & Government webpage	Website and Social Media
Type of support	Reading Materials and online lectures	Media library and Live webinars with health professionals	“One hour with AMD, SID and SIEDP”- Facebook page Physical activity and Diet by Government webpage	Online assistance by healthcare providers

improving the quality and duration of life, reducing costs and complications. Several studies have demonstrated the safety, efficacy, and cost effectiveness of this technological revolution³⁶. To achieve further benefits, extensive studies of these technologies are required. While many of the technological opportunities are now becoming available, an improved understanding of patient behaviors and lifestyle choices is needed in order to achieve the full potential for emerging digital health technologies for patients especially with diabetes³⁶.

Telehealth as defined by WHO, is the ‘delivery of health care services, where patients and providers are separated by distance. Telehealth uses Information and Communication Technology (ICT) for the exchange of information for the diagnosis and treatment of diseases and injuries, research and evaluation, and for the continuing education of health professionals. Telehealth can contribute to achieving universal health coverage by improving access for patients to quality, cost-effective and proper health services wherever they may be. It is particularly valuable for those in remote areas, vulnerable groups and ageing populations³⁷. People with diabetes are at risk even if not contracted with COVID-19. The healthcare setting due to COVID-19 lockdown and restrictions imposed like social distancing and isolation have posed problems for diabetics for regular health checkups and lifestyle modifications, like exercise and diet. Online mode of support, monitoring by health care professionals and consistent sensitization is important. Table 2 summarizes few attempts taken by countries who were worst affected by COVID-19, to help and support diabetics¹⁰.

Online initiatives (like some mentioned in the Table 2) must be taken into consideration and more surveys and researches need to be conducted to assess the feasibility and accessibility of these modes of health checkups and sensitization programmes to contain and maintain diseases like diabetes during

public health emergencies as posed by COVID-19 pandemic. More countries in South East Asia and other places are making policies to adopt such measures to help vulnerable patients specially those who do not live in vicinity of healthcare providers.

Conclusion

People with diabetes comorbidity should be treated as a vulnerable group in case of COVID-19 infection¹². T1DM and T2DM both are susceptible to infections and their associated complications. Diabetic comorbidity might increase the magnitude of the COVID-19 severity many fold as compared to non-diabetics³⁸. It is reported that the severity of the association of diabetes with COVID-19 ranges from 5 to 20%. Impaired humoral immunity with cytokine storm is a common phenomenon with COVID-19 infection, along with autoimmune risk of pancreatic β -cells which may pose a risk of developing new type of diabetes after COVID-19 virus infection. Maintaining regular health checkup and treatment of diabetes patients seem to be a matter of great concern in the current lockdown situation because of containment of COVID-19 pandemicity. Monitoring health conditions of diabetes patients through distant monitoring system like teleconsultation and telemedicine might play a pivotal role in the management of this disease in single and or with COVID-19 in combination. Globally, the diabetic people are of great concern and sensitive to COVID-19 infection. Focused interventions are needed to address the severity of COVID-19 with diabetic comorbidity.

Conflict of interest

All authors declare no conflict of interest.

References

- 1 WHO Constitution. [Cited 2020, August 15]. Available from: <https://www.who.int/about/who-we-are/constitution>.
- 2 WHO Coronavirus Disease Dashboard (COVID-19). [Cited 2020, August 15]. Available from: <https://covid19.who.int/>.

- 3 Noncommunicable diseases. [Cited 2020, August 15]. Available from: <https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases>.
- 4 IDF Diabetes Atlas 9th Ed. [Cited 2020, August 15]. Available from: <http://https://www.diabetesatlas.org/en/sections/worldwide-toll-of-diabetes.html>.
- 5 Gupta R, Hussain A, Misra A, Diabetes and COVID-19: evidence, current status and unanswered research questions. *Eur J Clin Nutr*, 74 (2020) 864.
- 6 Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, Yu X & Dong K, Clinical characteristics and outcomes of patients with severe COVID-19 with diabetes. *BMJ Open Diab Res Care*, 8 (2020) e001343.
- 7 Pal R & Bhansali A, COVID-19, diabetes mellitus and ACE2: The conundrum. *Diab Res Clin Pract*, 162 (2020) 108132.
- 8 Zhu L, She Z G, Cheng X, Guo J, Zhang BH & Li H, Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab*, 31 (2020) 1068.
- 9 Cariou B, Hadjadj S, Wargny M & Pichelin M, Al-Salameh A, Allix I, Coralie Amadou C, Arnault G, Baudoux F, Bauduceau B, Borot S, Bourgeon-Ghittori M, Bourron O, Boutoille D, Cazenave-Roblot F, Chaumeil C, Cosson E, Coudol S, Patrice Darmon P, Disse E, Ducet-Boiffard A, Gaborit B, Joubert M, Kerlan V, Laviolle B, Marchand L, Meyer L, Potier L, Prevost G, Jean-Pierre R, Robert R, Pierre-Jean S, Sultan A, Jean-François T, Thivolet C, Tramunt B, Vatiec C, Roussel R, Jean-François G & Gourdy P, Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia*, 63 (2020) 1500.
- 10 Hartmann BJ, Elizabeth ME, Goyder C, Kinton J, Perring J, Nunan D, Mahtani K, Buse JB, Prato S D, Ji L, Roussel R & Khunti K, Diabetes and COVID-19: Risks, Management, and Learnings From Other National Disasters. *Diab Care*, 43 (2020) 1695.
- 11 Rubino F, Amiel S A, Zimmet P, Alberti G, Bornstein S, Eckel RH, Mingrone G, Boehm B, Cooper ME, Chai Z, Prato SD, Ji L, Hopkins D, Herman W H, Khunti K, Mbanya JC, Renard E, New-Onset Diabetes in COVID-19. *N Engl J Med*, (2020) NEJM.org (downloaded on August 6, 2020).
- 12 Katulanda P, Dissanayake HA, Ranathunga I, Ratnasamy V, Wijewickrama PSA, Yogendranathan N, Gamage KKK, de Silva NL, Sumanatilleke M, Somasundaram NP & Matthews DR, Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. *Diabetologia*, 63 (2020) 1440.
- 13 Caruso P, Longo M, Esposito K & Maiorino MI, Type 1 diabetes triggered by COVID-19 pandemic: A potential outbreak? *Diab Res Clin Pract*, 164 (2020) 108219.
- 14 WHO Diabetes [Cited 2020, August 18] Available from: <https://www.who.int/news-room/fact-sheets/detail/diabetes>.
- 15 Unnikrishnan R, Pradeepa R, Joshi SR, Mohan V, Type 2 Diabetes: Demystifying the Global Epidemic. *Diabetes*, 66 (2017) 1432
- 16 Zolghadr L, Farahani BV, Ghasemzadeh H & Javadi N, Physicochemical studies of closed loop insulin delivery system based on intelligent carboxymethyl cellulose hydrogel. *Indian J Biochem Biophys*, 56 (2019) 125.
- 17 Mistry KN, Dabhi BK & Joshi BB, Evaluation of oxidative stress biomarkers and inflammation in pathogenesis of diabetes and diabetic nephropathy. *Indian J Biochem Biophys*, 57 (2020) 45.
- 18 Melkonyan AM, Guevorkyan AG, Alchujyan NKH, Hovhannisyanyan MR, Movsesyan NH, Hayrapetyan HL, Kevorkian GA & Aghajanova YM, Sex and age-related changes in L-arginine metabolism in peripheral blood leukocytes in young caucasians with type 1 diabetes mellitus. *Indian J Biochem Biophys*, 57 (2020) 339.
- 19 Ghosh S & Ghosh S, Air quality during COVID-19 lockdown: Blessing in disguise. *Indian J Biochem Biophys*, 57 (2020) 420.
- 20 Coronavirus disease (COVID-19) outbreak. [Cited 2020, August 15]. Available from: <https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19>.
- 21 Novel coronavirus structure reveals targets for vaccines and treatments. [Cited 2020, August 16]. Available from: <https://www.nih.gov/news-events/nih-research-matters/novel-coronavirus-structure-reveals-targets-vaccines-treatments>.
- 22 Muniyappa R & Gubbi S, COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab*, 318 (2020) E736.
- 23 Kumari NKP & Jagannadham MV, Organic solvent induced refolding of acid denatured heynein: Evidence of domains in the molecular structure of the protein and their sequential unfolding. *J Proteins Proteomics*, 2 (2011) 11.
- 24 Kumari NKP & Jagannadham MV, SDS induced molten globule state of heynein; a new thiol protease: Evidence of domains and their sequential unfolding. *Colloids Surf B Biointerfaces*, 82 (2011) 609.
- 25 Maddaloni E & Buzzetti R, COVID-19 and diabetes mellitus: unveiling the interaction of two pandemics. *Diab Metab Res Rev*, (2020) e33213321.
- 26 Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, Boehm B, Amiel S, Holt RIG, Skyler J S, DeVries JH, Renard E, Eckel RH, Zimmet P, Alberti GK, Vidal J, Geloneze B, Chan JC, Ji L & Ludwig B, Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diab Endocrinol*, 8 (2020) 546.
- 27 Cuschieri S & Grech S, COVID-19 and diabetes: The why, the what and the how. *J Diabetes Complications*, 34 (2020) 107637.
- 28 Fang L, Karakiulakis G, Roth M, Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *The Lancet*, 8 (2020) e21.
- 29 Means C, Mechanisms of increased morbidity and mortality of SARS-CoV-2 infection in individuals with diabetes: what this means for an effective management strategy. *Metab Clin Exp*, 108 (2020) 154254.
- 30 Gupta R, Ghosh A, Singh A K, Misra A, Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr*, 14 (2020) 211.
- 31 Pal R & Bhadada SK, COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. *Diabetes Metab Syndr*, 14 (2020) 513.
- 32 Bloomgarden ZT, Diabetes and COVID-19. *J Diabetes*, 12 (2020) 347.

- 33 Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S & Hu D, Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diab Metab Res Rev*, (2020) e3319.
- 34 Chee YJ, Huey Ng SJ & Yeoh E, Diabetic ketoacidosis precipitated by COVID-19 in a patient with newly diagnosed diabetes mellitus. *Diab Res Clin Pract*, 164 (2020)108166.
- 35 Palermo NE, Sadhu RA & McDonnell ME, Diabetic Ketoacidosis in COVID-19: Unique Concerns and Considerations. *J Clin Endocrinol Metab*, 105 (2020), 1.
- 36 Garg SK, Rodbard D, Hirsch IB & Forlenza GP, Managing New-Onset Type 1 Diabetes During the COVID-19 Pandemic: Challenges and Opportunities. *Diabetes Technol Ther*, 22 (2020) 431.
- 37 WHO Telehealth [Cited 2020, August 18]. Available from: <https://www.who.int/gho/goe/telehealth/en/>.
- 38 Kumar A, Arora A, Sharma P, Anikhindi S A, Bansal N, Singla V, Khare S & Srivastava A, Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr*, 14 (2020) 535.
- 39 Mantovani A, Byrne C D, Zheng M H & Targher G, Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis*, 30 (2020) 1236.