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Diabetes and COVID-19: a major challenge in pandemic period?

C. CHAKRABORTY[1,2], A.R. SHARMA[2], M. BHATTACHARYA[2], G. SHARMA[3], G. AGORAMOORTHY[4], S.-S. LEE[2]

[1]Department of Biotechnology, School of Life Science and Biotechnology, Adamas University, Kolkata, West Bengal, India
[2]Institute for Skeletal Aging & Orthopedic Surgery, Hallym University-Chuncheon Sacred Heart Hospital, Chuncheon-si, Gangwon-do, Republic of Korea
[3]Neuropsychopharmacology and Toxicology Program, College of Pharmacy, Kangwon National University, Republic of Korea
[4]College of Pharmacy and Health Care, Tajen University, Yanpu, Pingtung, Taiwan

Chiranjib Chakraborty and Ashish Ranjan Sharma contributed equally

Abstract. – OBJECTIVE: Diabetes is a lifestyle disease and it has become an epidemic worldwide in recent decades. In the ongoing COVID-19 pandemic situation, diabetes has become a serious health concern since large numbers of patients are vulnerable to die from the virus. Thus, the diabetic patients affected by COVID-19 cause a major health crisis now. Reports show that large occurrence of diabetes makes it a serious comorbidity in COVID-19 patients.

MATERIALS AND METHODS: It is crucial to understand how COVID-19 affects diabetes patients. This paper has reviewed published literature extensively to understand the pattern, importance, care, and medication.

RESULTS: This review summarizes the association between COVID-19 and diabetes in terms of susceptibility for pneumonia and other diseases. It also discusses the harshness of COVID-19 with diabetes populations and immunological impacts. It further adds the ACE2 receptor role in diabetes with COVID-19 patients.

CONCLUSIONS: Finally, this paper illustrates different types of diabetes management techniques, such as blood glucose management, self-management, mental health management, and therapeutic management. It also summarizes the current knowledge about diabetic patients with COVID-19 to fight this pandemic.

Key Words:
Diabetes, COVID-19, Risk factor analysis, Therapeutic choice.

Introduction

The COVID-19 pandemic continues to impact the world. It has spread across over 200 countries and threatening the lives of millions[1,2]. When it originated from Wuhan (China) at the end of 2019, it caused pneumonia for unknown reasons[3,4]. Then, scientists in China were able to isolate a new strain of coronavirus entitled 2019-nCoV on 7 January 2020. It was later renamed as SARS CoV-2. On 12 January 2020, the genome sequence of the 2019-nCoV was published from China[5,6]. Two weeks later, the WHO declared it as a global health emergency. It now affects over 34.8 million people, including 1.03 million deaths till 4 October 2020. It is spreading across healthy populations and also affecting patients with chronic diabetes and cardiac vascular diseases[7,8].

Diabetes mellitus (DM) affects people throughout the world, especially in developing countries[9]. Presently, diabetes and COVID-19 are considered as a major global health concern. Evidence relating to the impact of diabetes and COVID-19 is limited in literature. Whether the diabetes patients have an increased inclination towards COVID-19 or not is not clear. However, the risk factors result in higher mortality for diabetes and COVID-19 patients. When the patients are elderly, the risk factors are the highest for diabetes and COVID-19 and additional mortality risk are reported for the elderly diabetes

Corresponding Authors: Chiranjib Chakraborty, Ph.D; e-mail: drchiranjib@yahoo.com
Govindasamy Agoramoorthy, Ph.D; e-mail: agoram@tajen.edu.tw
Sang-Soo Lee, MD, Ph.D; e-mail: 123sslee@gmail.com

and COVID-19 patients[10]. Clinical data on diabetes and COVID-19 initially came from China. The published papers show some general comorbidity in COVID-19 patients and they include chronic obstructive pulmonary disease, type 2 diabetes mellitus (T2DM), arterial hypertension, cardiovascular diseases (CVD), obesity, etc.[11,12]. Papers have shown severe COVID-19 patients with comorbidities that include hypertension, T2DM, CVD, obesity, and renal disease[13,14]. This review also includes various published papers on diabetes and COVID-19 originating from many countries.

It is still unclear whether or not the diabetes populations are more susceptible to COVID-19. Report shows that diabetes populations experiencing increased risk of infection so at this angle, the COVID-19 may pose a threat to life[15]. Hospital data from China showed 7.8% to 9.7% patients with diabetes among the COVID-19 patients initially[16,17]. While analyzing the published data, we have seen high percentage of diabetes among COVID-19 patients. However, the percentages of diabetes vary in different reports due to variations in factors, such as populations between countries and hospitals (Table I).

This review attempts to provide an in-depth analysis of diabetes with COVID-19 patients on the susceptibility for pneumonia and other diseases in various populations across cohorts. It presents the dangers of COVID-19 in diabetes populations with immunological impacts. Similarly, the role of ACE2 in diabetes with COVID-19 patients has been illustrated. Finally, it presents appropriate management techniques that include blood glucose management, self-management, mental health management, therapeutic management for diabetes with COVID-19 patients in the continuing pandemic situation.

Diabetes and COVID-19: Increased Susceptibility for Diseases

Diabetes Patients Susceptible for Different Diseases

Diabetes patients are not only susceptible to a range of infections caused by different causative agents such as bacteria and fungi. Compared to non-diabetic patients, they are prone to other diseases[18,19]. A range of mechanisms may be responsible for the vulnerability as well as severity of infections. A weakened polymorph nuclear function has been observed in diabetic patients[12,20]. Dysregulation of nitric oxide (NO) production and impairment of T lymphocyte function has also been noted[21,22]. The T2DM patients are also linked with reduced host defense immunity and therefore, the patient-pools are further susceptible to infections[23].

Diabetes Patients Susceptible For Viral Diseases

Generally, the IFN and pro-inflammatory cytokines are secreted by cell as a physiological response during viral infection and replication to stop the infection and replication. Research[24] has shown that the T2DM patients have reduced production of IFN-α, and it decreased the antiviral response. Therefore, diabetes patients may be more susceptible for viral diseases.

Elevated Blood Glucose and Viral Replication

Increased blood glucose levels could augment glucose concentrations that help in the airway secretion[25]. *In vitro* experiments have shown that high glucose concentrations infect pulmonary epithelial cells leading to increase influenza virus infection and replication[26]. This study suggests that elevated blood glucose level increase the viral replication *in vivo*. It also shows that increased glucose levels may repress the anti-viral immune response[27]. Conversely, Philips et al[28] using animal model reported that diabetes related with changes of lung structure by increasing the permeability of the vasculature and aiding to collapse the alveolar epithelium.

Hu et al[29] show that hyperglycemia lowering the IFN-1 secretion. In this study, researchers have used the peripheral blood mononuclear cells (PBMC) to understand the immune cell respond. Authors observed augmented glucose levels leading to the secretion of other pro-inflammatory cytokines. Thus, T2DM could change in the innate immune system with high glucose levels causing impaired host defense mechanism against viral disease.

Diabetes Patients Susceptible For Pneumonia and Influenza

Diabetes patents are often prone to pneumonia and influenza. In a cohort study of 2,931 pneumonia patients with type 2 diabetes, Kornum et al[30] showed higher mortality compared to other patients. As a result, scientists recommended immunization of pneumococcal and influenza vaccines for diabetes patients[23]. During SARS outbreak, diabetes patients were more prone to pneumonia, morbidity and death[31]. Similarly, during the MERS outbreak, 32 victims were found to suffer from diabetes and hypertension further destabilizing the immune system[32].

Table I. Patients population analysis report of COVID-19 with diabetes.

Sl. no	Reference	Country	Patients population size	COVID-19 patients with diabetes	Remark
1	Yang et al[36]	China	52 patients	17%	High mortality rate was observed of intensive care unit patients having diabetics with COVID-19
2	Deng et al[37]	China	26 patients	42.3%	Comorbidity was noted from different patients having diabetic, hypertension, coronary heart disease, as well as cerebral infarction with COVID-19
3	Guan et al[38]	China	1,099 patients	14%	The study showed diabetic increase risk of different diseases in the patient's and where death has been noted in COVID-19 patients
4	Zhang et al[39]	China	140 patients	12%	Comorbidity was observed in diabetic patients with COVID-19
5	Wuet al[40]	China	72,314 patients	7.3%	Case-fatality rate was calculated in this study
6	Li et al[75]	China	1527 patients	9.7%	It has been noted that patients with COVID-19 and other diseases (such as hypertension, cerebrovascular disease and diabetes) may develop severe condition
7	Onder et al[41]	Italy	355 patients	35.5%	Study analyzed the case-fatality rate in Italy
8	Qin et al[76]	China	280 patients	10%	Diabetic patients with COVID-19 need more care and supervision
9	Mercuro et al[77]	USA	90 patients	28.9%	Comorbid conditions are most common in this type of patients
10	Lian et al[78]	China	788 patients	13.84%	Older COVID-19 patients exhibited significantly higher percentage of comorbidities as well as higher rate of other disease
11	Zhou et al[13]	China	191 patients	19%	Higher rate of organ failure and subsequent mortality was observed in COVID-19 patients due to older age
12	Guo et al[79]	China	187 patients	28%	COVID-19 patients significantly allied with myocardial injury and others cardiovascular diseases.
13	Huang et al[4]	China	41 patients	20%	In this work researchers performed epidemiological study, but not included effect of diabetes or cardiovascular disease
14	Chen et al[80]	China	274 patients	17%	Acute respiratory failure, sepsis, heart failure, and cardiac injury were the maximum in case of critical COVID-19 patients
15	Shi et al[81]	China	416 patients	14%	COVID-19 patients with common cases of cardiac injury
16	Wang et al[82]	China	1012 patients	27%	In old age, diabetes patients with COVID-19 were having all risk factors cardiovascular diseases

Table continued

Table I. (Continued). Patients population analysis report of COVID-19 with diabetes.

Sl. no	Reference	Country	Patients population size	COVID-19 patients with diabetes	Remark
17	Guan et al[83]	China	1590 patients	8%	Diabetes and COVID-19 were the main risk factors for intensive care unit patient
18	Guo et al[84]	China	174 patients	21%	Diabetes patients having higher levels of biomarkers (CRP, IL-6 etc.)
19	Wang et al[85]	China	138 patients	10%	Research not included the effect of diabetes and COVID-19
20	Wu et al[86]	China	201 patients	11%	Diabetic patients of older age with COVID-19 was associated with higher risk of Acute Respiratory Distress Syndrome
21	Liu et al[87]	China	137 patients	10%	Epidemiological research was not included the consequences of diabetes
22	Bhatraju et al[88]	USA	24 patients	58%	Higher mortality among hypoxemic respiratory failure of critical COVID-19 patients with diabetic
23	Goyal et al[89]	USA	393 patients	25%	COVID-19 patients with obesity was common and having risk factor for respiratory failure
24	Simonnet et al[90]	France	124 patients	23%	Disease severity increased for obesity of diabetic with COVID-19 patients
25	Cao et al[91]	China	102 patients	11%	Higher age of COVID-19 patients with high mortality rate
26	Ruan et al[92]	China	150 patients	17%	COVID-19 cases included age, secondary infection and presence of underlying diseases, fulminant myocarditis
27	Mo et al[93]	China	155 patients	10%	COVID-19 patients had older age showing more underlying comorbidities with higher incidence of bilateral pneumonia and pleural effusion
28	Mao et al[94]	China	214 patients	14%	Diabetic patients with COVID-19 frequently have neurologic manifestations
29	Feng et al[95]	China	476 patients	10%	Multiple organ dysfunction and impaired immune function of diabetic patients with severe COVID-19
30	Shen et al[96]	China	119 patients	10%	Damage of kidney, liver, heart of COVID-19 patients with diabetic were noted
31	Du et al[97]	China	179 patients	18%	High death rate of pre-existing cerebrovascular and cardiovascular or disease containing COVID-19 patients with diabetes
32	Fadini et al[98]	Italy	355 patients	35.5%	The association between high mortality and diabetes from any acute and chronic condition, including COVID-19 infections
33	Kumar et al[99]	India	16003 patients	9.8%	Mortality was two-fold higher as well as severity of COVID-19, as compared to non-diabetics patients
34	Sardu et al[100]	Italy	59 patients	44%	COVID-19 with hyperglycemia and diabetes had an increased risk of severe disease
35	Grasseli et al[101]	Italy.	1519 patients	17%	COVID-19 and diabetics patients were critically monitor in Italy

COVID-19 and Diabetes Populations in Different Cohorts

Community testing is inadequate for COVID-19 across many countries, so data on the community-based diabetes and COVID-19 is low. After hospitalization, patients are being monitored and all clinical parameters are tested. Therefore, information about hospitalized patients is available on COVID-19 and diabetes patients (Table I). However, the percentage of COVID-19 and diabetes patients varies from 7.3% to 58%[33,34]. We have observed wide difference between published studies that vary across countries, populations and hospitals. Other factors, such as sample size, age of patients, ethnic and racial background also contribute for the variations. So, more accurate data are needed. From our analysis (Table I), we have seen a study with the highest number of sample sizes (16003 patients from 33 study areas) and it showed 9.8% COVID-19 patients with diabetes[35]. Similarly, another study analyzed larger sample size (1527) with 9.7% COVID-19 patients with diabetes[17].

Among 32 non-survivors from a batch of 52 ICU patients, 22% of them had diabetes and another 22% with cerebrovascular diseases[36]. Another study[37] has showed 26 COVID-19 fatalities with dangerous comorbidities at Wuhan and it reported significant comorbidities with diabetes, hypertension, coronary heart disease, and cerebral infarction. The comorbidity of diabetes alone reached to 42.3%. In China, among a group of 1099 COVID-19 positive cases, 173 showed severe diabetes hypertension, heart and cerebrovascular diseases with 16.2% diabetes alone[38]. Likewise, in a group of 140 patients hospitalized in China for COVID-19, 12% showed known history of diabetes[39]. Another report[40] with 72,314 COVID-19 patients from the China CDC showed high mortality among patients suffering from diabetes where the overall mortality was 2.3% and mortality from diabetes combined COVID-19 showed 7.3%.

The Diabetes Populations Can Suffer Severe COVID-19 Illness

As shown above, the COVID-19 patients with known history of diabetes are more vulnerable for infections; complications and sometime mortality have been found[8,38,41,42]. In Hong Kong, mortality were observed in elderly patients (aged 75) with diabetes and pneumonia[43]. Similar type of mortality was found among previous coronavirus infection with diabetes[44,45]. The Chinese CDC states that diabetes patients had higher mortality rates (7.3%) compared to the overall COVID-19 infected population (2.3% of 72,314 patients)[33]. Guo et al[46] showed the risk of diabetes and COVID-19 with 174 COVID-19 confirmed patients and they found diabetes to be the risk factor for pneumonia. Similarly, another study analyzed 52 ICU patients with COVID-19 and 22% of them were diabetic. Among 52 COVID-19 ICU admitted patients, 32 patients died[36,47]. Chen et al[10] found 904 COVID-19 patients of which 136 were diabetes patients. They described high blood glucose as the risk factor for mortality. They also found hypertension as the other risk factor.

Scientists have found possible vulnerability for COVID-19 among individuals with diabetes due to following causes. First, SARS-CoV-2 has higher receptor binding affinity (ACE2 receptor) providing efficient entry of virus into the cell. Second, SARS-CoV-2 may have less viral clearance from cell so the viral load becomes high in the body. Third, the T cell function may be reduced due to virus. Fourth, the susceptibility to inflammation may be increased after viral entry. Fifth, cytokine secretion and cytokine storm syndrome may become a morbidity cause. Finally, the presence of cardiovascular disease may increase the morbidity of diabetes patient[48].

Immunological Impacts

Hyper-inflammatory condition has been found in diabetes patients. A chronic inflammatory condition is noted in diabetes patients characterized by multiple metabolic abnormalities, as well as vascular abnormalities. In type 1 diabetes (T1D), T cell abnormalities are one of the significant causes for the destruction of the pancreatic islets[49]. In T2D, the inflammation may increase the risk of other diseases[50]. T2D is notable by insulin resistance associated to the inflammation of pancreatic cell. Also, cytokine-mediated insulin resistance is observed in T2D[51]. Low-grade inflammation is common in diabetes. Scientists have reported that intracellular bacterial infection is one of the risk factor for diabetes[52], so SARS CoV-2 pathogen is also a risk factor for diabetes. Similarly, in MERS-CoV patients, the virus activates human T cells[53]. After MERS-CoV infection, the disease impacts harshly in diabetic mice in experiments leading to abnormal cytokine response and change in CD4+ T cell counts with an elevated level of cytokine IL17a[54]. Inflammation in COVID-19 patients with the high levels of

different cytokines especially pro-inflammatory cytokines includes interleukin-6 (IL-6) with elevated levels of C-reactive protein[55]. Mehta et al[56] also show 'Cytokine Storm' in patients with COVID-19.

Actually, CD4 T lymphocytes are quickly triggered to become pathogenic T helper-1 cells. Subsequently, it leads to the secretion of high quantity inflammatory cytokine entitled as "cytokine storm". The augmented expression of IL-6 and other cytokines create the "cytokine storm"[57]. The CD4+ T helper cells regulate antigen production and immunity against coronavirus through interferon gamma production[58]. Recently, Chen et al[59] analyzed the immunological characteristics of severe COVID-19 patients with augmented levels of IL-6, IL-10, and TNFα. They also found low number of T cell populations (CD4+T and CD8+T cells) and absolute numbers of T lymphocytes compared to patients who are having moderate COVID-19 disease.

ACE2 for Diabetes With COVID-19 Patients

A similarity of receptor binding was reported among SARS-CoV and SARS-CoV-2. Both SARS-CoV and SARS-CoV-2 interact with target cells through ACE2 receptor to catapult the viral entry into target cells[60,61]. ACE2 receptor is overexpressed in different epithelial cells, such as lung, kidney, intestine, heart, cerebral neurons, immune cells, pancreas and blood vessels[62,63]. This receptor changes the angiotensin II into angiotensin-$^{1-7}$ peptide and it supports in vasodilation. Conversely, ACE2 has an important role in anti-oxidation and anti-inflammation in normal physiological condition. The ACE2 inhibitors can be used as a therapy for the management of patients suffering from T1D and T2D[64] to increase the ACE2 receptor expression. Fang et al[7] have hypothesized that ACE2-interacting therapy may augment the risk for developing lethal COVID-19.

In the laboratory diabetic mice, increased amount of ACE2 expressions were found in pancreas, renal cortex, and liver. It is presumed that the ACE2 might be highly expressed in people with diabetes and COVID-19[65]. Cristelo et al[65] postulated that for diabetic patients, the ACE2 can act in two ways. Bindom et al[66] have shown that there is a significant role of ACE2 in the improvement of glycemia levels in diabetic mice with direct effect in pancreas. Thus, it may improve insulin sensitivity causing glucose-mediated insulin release[67] by helping the reduction of T2DM development[68].

Management of Diabetes and COVID-19 Patients

Monitoring of Blood Glucose Level

Blood glucose level should be kept under control for patients suffering from diabetes and they must keep good glycemic control. Zhou and Tan[69] did blood glucose test among 29 diabetes and COVID-19 patients with a total of 881 capillary blood glucose tests and it showed 56.6% with irregular blood glucose levels. It included 29.4% pre-prandial blood glucose tests and 64.5% of post-prandial tests. Limited studies are available addressing the role of blood glucose level in diabetes patients during COVID-19 treatment. A recent study emphasized to control the blood glucose level during treatment and it recommended subcutaneous delivery of insulin for the diabetes patients with COVID-19[70]. Similarly, Wang et al[71] advised proper blood glucose management. Hence, frequent monitoring of the blood glucose levels is needed.

Self-Management

Limited data are available on the self-management of patients suffering from diabetes and COVID-19. Some online information is available, but they are insufficient. Some web-based applications or mobile phone apps are available to support the diabetes with COVID-19 patients[40]. However, it is necessary to self-monitor blood glucose level for diabetes with COVID-19 patients. Disciplined physical exercise should be increased, especially for those with the history of diabetes as shown in Figure 1. Other preventive measures such as maintenance of proper health and hygiene, proper consumption of vitamin and minerals, such as vitamins (C, D), Zinc, and other antioxidant molecules should be taken with care.

Mental Health Management

The mental health is a major concern in the pandemic period[72]. The COVID-19 and diabetic patients more are susceptible to serious mental health problems as compared to the general population[73]. Therefore, it is necessary to pay additional attention to mental health of COVID-19 and diabetic patient population.

Therapeutic Management

There are several types of treatments for the diabetes and COVID-19 patients as shown in Figure 2. However, the therapeutic intervention can be applied after understanding the exact condition of patients. Metformin is an important choice

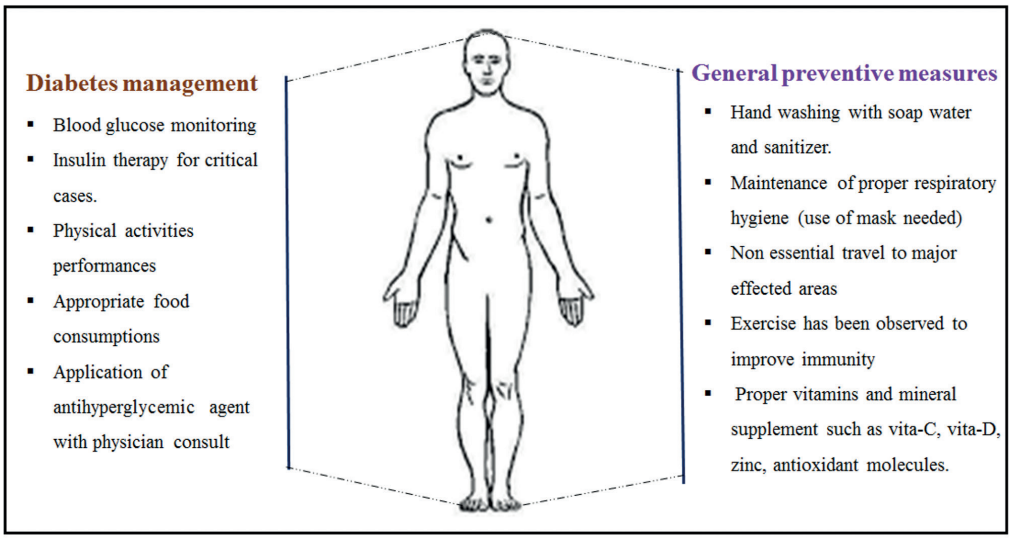

Figure 1. Diabetes management during COVID-19 in pandemic period.

Table II. A list of therapeutic choices for COVID-19 and diabetes patients.

Sl. no	Therapeutic option for COVID-19 and diabetes patients	Remark	Reference
1	Metformin	Metformin activate the AMP-activated protein kinase in the specific organ like liver. That enhanced the overexpression of ACE2 and phosphorylated. This phenomena leads to reduce this viral particle binding. This molecule decreases the creation of oxidative stress, DNA damage, and ROS.	(102-104)
2	Sodium-glucose cotransporter 2 (SGLT2) inhibitor	SGLT2 inhibitor increases the ACE2 protein expression, which leads to rise in angiotensin (1-7) peptide formation. It is helps to vasodilation and reduce inflammation into the lungs. It also prevents the secretion of proinflammatory cytokines.	(105-107)
3	Thiazolidinediones (TZD)	TZD inhibit pro-inflammatory cytokines including the secretion of IL-6. It also reduced the ACE-1, angiotensin-2 production and augment the circulating ACE2 concentration. It also increased angiotensin (1-7) peptide formation.	(108, 109)
4	Dipeptidyl peptidase-4 (DPP4) inhibitors	DPP4 inhibitors showed anti-inflammatory effects in COVID-19 patients. The effects of glucose lowering through GLP-1 production.	(110)
5	Glucagon like peptide receptor agonists (GLP-1RA)	GLP-1RA has anti-adipogenic as well as anti-inflammatory effects. It may decreases inflammatory condition of COVID-19 patients through the activation of NF-κB and AMPK.	(111-113)
6	ACE inhibitors (ACEi) and Angiotensin-receptor blockers (ARB)	ACEi reduces this virus infection to ACE2 blocking. The ACEi and ARB reduces organ fibrosis and endothelial injury, balance insulin sensitivity along with the cellular energy metabolism.	(114-116)

for COVID-19 and diabetic patients. The SGLT2 inhibitors can also be used for acute illness of COVID-19 and diabetes. The glucagonlike peptide 1 receptor agonists or DPP-4 inhibitors may be used as a therapeutic option for the hospitalized patients. Several therapeutic choices are shown in Table II. The hypovitaminosis D is a probable risk factor for insulin resistance[74], so vitamin D supplements are prescribed by physicians to treat diabetes to maintain glycemic control[43,76].

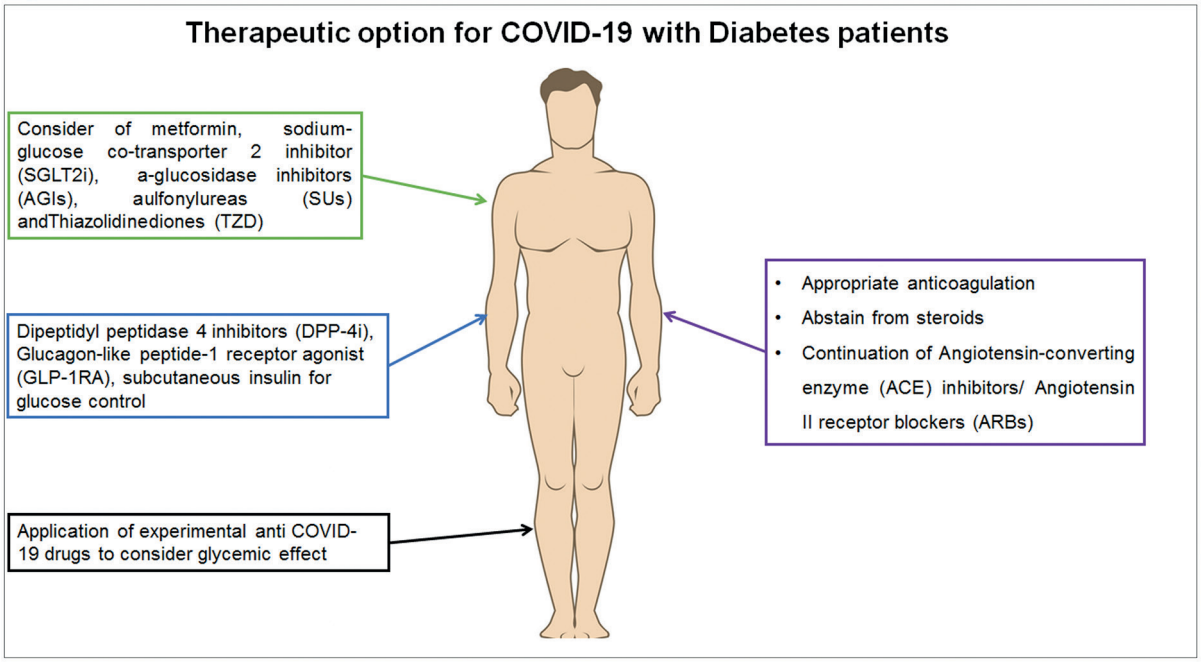

Figure 2. Therapeutic choices for COVID-19 and diabetes patients.

Conclusions

It appears that the pandemic may prolong and the vulnerable diabetes and COVID-19 patients may continue to face challenges. The developing countries may encounter more problem due to high rate of diabetes. For example, the world's two highly populated countries, China and India, have millions of diabetes patients and the threat is real. Also, the COVID-19 infection is spreading at a higher rate among people in developing countries and India has recently admitted social transmission with over 6.5 million cases and over 100,000 deaths. The COVID-19 has become a mirror to understand the health care systems of all countries. This review shows some noticeable absences. The mechanism of action in cellular and molecular level in the COVID-19 patients with diabetes is not properly understood. Therefore, we call for a multidisciplinary research comprising renowned pulmonologists, endocrinologists, immunologist and molecular biologists. Detailed research is needed to address all unanswered queries on the impact of COVID-19 to patients with diabetes. Then, clinical management of patients suffering from diabetes and COVID-19 will become easier. In-depth therapeutic management for diabetic patients is needed in respect to COVID-19 that includes asymptomatic patients, moderate and severe patients. There is an urgent need to understand the post survival effect for diabetes and COVID-19 patients since detailed data from all countries are not available.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Approval of Studies and Informed Consent

Not required.

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Author Contributions

Conceptualization; Data curation; Writing - original draft: Chiranjib Chakraborty, Writing, Validation; Visualization: Ashish Ranjan Sharma, Manojit Bhattacharya, Garima Sharma, Sang-Soo Lee, Writing, review and editing: Govindasamy Agoramoorthy.

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