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Understanding the Interplay between COVID-19 and Diabetes Mellitus

Walaa Mohammedsaeed[1], Saiema Ahmedi[2], Nikhat Manzoor[2]

[1]Department of Medical Laboratories Technology, Faculty of Applied Medical Sciences, Taibah University, Al Madinah Al Munawarah, KSA
[2]Department of Biosciences, Jamia Millia Islamia, New Delhi, India
Email: nikhatmanzoor@yahoo.co.in, wmohammedsaeed@taibahu.edu.sa

Abstract

COVID-19 pandemic has shown greater severity in people with co-morbidities; diabetes being the leading cause of higher mortality rates in COVID-19 patients. Besides compromised immunity, there are other factors that make diabetics more prone to SARS-CoV-2 infection. To date, there is no clinically proven treatment for this disease, but fortunately there are several reports of vaccines in different stages of development. This review compiles some commonly used anti-diabetic drugs and their probable efficacy during a COVID-19 attack. This is also an attempt to understand the cause of severity of SARS-CoV-2 infection in diabetic patients. Until a proper cure or approved vaccine is available, it is best to manage the disease by improving the immune status and making use of already available drugs that show potential against the virus.

Keywords

COVID-19, SARS-CoV-2, Diabetes Mellitus, Anti-Viral Potential of Anti-Diabetic Drugs

1. Introduction

The year 2020 started with the onset of a viral infection called the novel corona virus disease (COVID-19), caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The first case was reported in December 2019 and the disease was declared a pandemic by March 2020. The virus has spread worldwide infecting millions of people to date [1]. Fortunately, the recovery rate is high and the death rate is low. Although only a few people become critically ill, the virus is a huge problem for people having a weak immune system. They in-

clude the elderly and people with pre-existing medical conditions, the most prevalent being hypertension and diabetes mellitus followed by cardiovascular diseases and respiratory diseases [2]. Besides commonly visible symptoms that include fever, dry cough, fatigue and dyspnoea, patients can also encounter pain, sore throat, diarrhoea, conjunctivitis, headache, loss of taste or smell, skin rashes, and/or discolouration of fingers or toes. Interestingly the disease may or may not be symptomatic and the symptoms, if any may take up to 2 - 14 days to become visible. The virus spreads in the form of droplets dispersed in the air while an infected person coughs, sneezes and even talks. This pathogen can survive on surfaces the duration varying from a few hours up to a few days depending on the environmental conditions and the type of surface [1].

Although scientists and doctors worldwide are working hard to prepare effective vaccines and drugs, unfortunately, to date there is no specific treatment available for COVID-19. The only best option is prevention and management that includes travel restrictions, patient isolation, and supportive medical care. The present review is an attempt to understand COVID-19 and its interplay with diabetes mellitus. Since, this virus is novel, not much has been reported regarding its severity in patients having pre-existing non-communicable diseases like diabetes. For better treatment strategies, it is pertinent that we understand the reasons for the development of COVID-19 complications in immunocompromised patients. Since there are no effective treatment options for COVID-19, doctors have been prescribing drugs that are either approved for other conditions or have been tested against viral infections other than SARS-CoV-2.

1.1. SARS-CoV-2 and COVID-19

Coronaviruses are a group of large, enveloped, RNA viruses. Their genome (27 - 32 kb) is packed inside a helical capsid formed by nucleocapsid proteins enclosed within another envelope. At least three structural proteins are found associated with the viral envelope. The membrane proteins and the envelope proteins are involved in the assembly of viral bodies. The spike proteins form surface protrusions giving a crown-like appearance to the virus and help in the entry of virus particles into the host cells. They also help in deciding which host to invade and are majorly responsible for the induction of host immune responses. Understanding the structure and function of spike proteins, and their interaction with the host, will help in the management of SARS-CoV-2 infection. Several coronaviruses also encode an envelope-associated hemagglutinin-esterase protein [3]. The spike proteins of SARS-CoV-2 fit into the ACE2 receptors (angiotensin-converting enzyme 2) present on human cell surfaces initiating a structural change that causes the fusion of viral membranes with the host cell membranes. This allows the entry of viral genes into the host cell where they are replicated into multiple copies producing manifold viruses. The genome sequence has been published and tremendous research work is going on throughout the world to unravel the mechanism of infection and an effective cure for

this contagious disease [4] [5]. The structure of spike proteins are specifically studied using different techniques like cryo-electron microscopy. These proteins are potential antiviral targets. Studies have shown that the SARS-CoV-2 spikes have 10 - 20 times more binding affinity for ACE2 receptors on human cell surfaces in comparison to the spikes from the 2002 SARS virus. This may be the reason for the rapid contagious spread of this new virus of 2019. Although the structure and sequence of the spikes of both 2002 SARS virus and SARS-CoV-2 are similar, the antibodies generated against the old virus were unable to successfully bind to the spikes of the new virus suggesting that completely different antibody based treatment strategies would be required [6].

Understanding the infection mechanism by which the virus invades and damages the human host are crucial to the identification of therapeutic and diagnostic strategies so that the disease can be predicted before it becomes fatal. Several studies have been reported that attempt to explain the mechanism of SARS-CoV-2 infection. It has been suggested that the infection mechanism involves binding of the virus to the ACE2 receptors present on epithelial cells of the host lungs, kidney, intestine and blood vessels and their consequent internalization. In fact the severity of the disease has been linked to type 1 integral membrane glycoproteins. There are two forms of ACE2 receptors—glycoproteins and metalloproteases. The membrane-bound glycoproteins contain a transmembrane domain and an extracellular domain while metalloproteases are soluble and are secreted outside [7]. The significance of soluble circulating ACE2 is not clear, but studies suggest that their levels increase in chronic diseases such as diabetes, chronic kidney diseases, and hypertension [8]. The substrates for ACE2 include kinins, apelin, neurotensin, dynorphin, ghrelin, amyloid, and angiotensin. It regulates angiotensin II (Ang II) by converting Ang I into Ang-(1-9), and degrading Ang II into Ang-(1-7), a vasodilatory and anti-proliferative peptide which protects the tissues [9]. Besides ACE2, SARSCoV-2 uses the TMPRSS2 (transmembrane protease serine 2) gene for spike protein priming. Both the genes are expressed in the lungs, epithelial cells of small intestine, upper oesophagus, liver, colon, blood vessels, heart, kidneys, and the gonads. Since the receptors are widely distributed on several organs and tissues, the infection could cause multiple organ failure [9] [10] [11].

Studies suggest that the virus attacks the haemecomponent of the β chain of haemoglobin dissociating the iron to form the porphyrin and reduces the capacity of haemoglobin to carry oxygen and carbon dioxide [12]. Another more accepted mode of infection points towards the inflammatory cascades, cytokine storms, and activation of coagulation cascades on entry of the virus into the human body. These cascades lead to severe and often fatal complications, such as sepsis, disseminated intravascular coagulation (DIC), and acute cardiovascular events [13].

1.2. Impact of COVID-19 on Diabetes Mellitus

Diabetes is a metabolic disorder that can lead to serious complications, such as

heart disease, stroke, retinopathy, nephropathy, and neuropathy. If uncontrolled, it can lead to blindness, kidney failure and lower-limb amputations. The disease results due to insufficient insulin secretion and/or insulin resistance. This chronic disease is one of the principal causes of morbidity and mortality throughout the world. At present 10.5% of the U.S. population is diabetic [14]. According to WHO, the rate of diabetes in Saudi Arabia is the second highest in Middle Eastern countries, and seventh in the world [15]. Approximately 463 million people, in the age group of 20 - 79 years, were estimated to be living with diabetes last year in 2019 [16]. Diabetes was presented as a risk factor for mortality in virus infected patients during 2002-2004 Severe Acute Respiratory Syndrome (SARS) coronavirus, 2009 swine flu pandemic (Influenza A H1N1), and 2012 Middle East Respiratory Syndrome-related coronavirus (MERSCoV) [17] [18]. It has been shown that COVID-19 deteriorates dysglycemia in diabetic patients [19].

Innate immune response, the first line of defence against SARS-CoV-2, is compromised in patients with uncontrolled diabetes, and hence the virus proliferates easily in the host without any hindrance. Moreover, there is an exaggerated cytokine response which leads to overproduction of pro-inflammatory cytokines, particularly interleukins IL-1, IL-6 and tumour necrosis factor-α. Similarly, patient with chronic obstructive pulmonary disease, have low levels of cytokine production, specifically interferon-*β*. This weakens host defence against coronavirus [19]. Besides, the activation of renin angiotensin system (RAS) contributes majorly to diabetic complications and blocks the vasoconstrictor and hypertrophic activity of Ang II. These mechanisms slow down the progression of diabetic complications but do not completely prevent it. The presence of ACE2 receptors in the heart and kidney make the RAS even more complex and are the basis to investigate the role of this enzyme in pathophysiological conditions and vascular complications of diabetes. Hence both ACE and ACE2 may play a vital role in modulating equilibrium between vasoconstrictors and vasodilators inside the heart and kidney but are counter-regulatory to each other. The role of ACE2 in diabetes is relatively unknown. Further studies can help in the development of new drugs that affect ACE2 activity and expression. These novel compounds may have immense clinical significance in the prevention and management of diabetic complications [20].

Studies suggest that poor prognosis of diabetes in COVID-19 patients is due to several factors that include compromised innate immunity, inflated cytokine response, reduced expression of ACE2 and use of drugs that interfere with RAS in diabetic patients. Glucose levels remain uncontrolled in these patients as *β*-cells are damaged, insulin develops resistance, and potassium levels drop (hypokalemia). Antiviral drugs like corticosteroids, lopinavir, ritonavir when administered for the treatment of COVID-19 make the situation worse in people with diabetes mellitus. The interplay between both diseases is such that COVID-19 causes dysglycemia of patients to deteriorate and diabetes mellitus

exacerbates the severity of the viral infection [19]. Upregulation of ACE2 seems to facilitate COVID-19 infection but interestingly the overall ACE2 expression is reduced in patients with diabetes due to the drugs that are commonly prescribed to patients. These drugs are often ACE inhibitors and angiotensin receptor blockers [21]. Hence, ACE2-stimulating drugs may be the primary cause of severity of COVID-19 disease observed in patients with metabolic co-morbidities [19].

1.3. Management and Preventive Measures

Diabetes is increasing at an alarming rate in most countries. The United States has the highest prevalence among developed nations. Qatar, Saudi Arabia, and Kuwait are all in the top 10. China and India have the highest numbers, 110 million and 69 million, respectively [16]. With such large numbers at stake, it becomes imperative that management and prevention strategies be developed for diabetics and other patients with pre-existing conditions during pandemics like COVID-19. Besides thorough hand-washing with soap and water and maintaining respiratory hygiene, diabetic patients should keep their glucose levels under control so that their immunity remains boosted. According to Pal and Bhadada, Calcium channel blockers may be a feasible option instead of ACE inhibitors as they do not upregulate ACE2 levels [19]. It is of utmost importance that diabetic patients maintain good glycaemic control in order to reduce both the risk of infection and the severity of the disease. This can be done by regularly monitoring blood glucose levels. With proper nutrition the body is more apt in fighting the infection. Care should be taken that the patient is not deficient in minerals and vitamins. There are several reports that claim that exercise plays a big role in improving immunity. General preventive measures advised worldwide include covering mouth while coughing/sneezing, avoid touching of mouth, nose, and eyes, and wearing appropriate face masks. These instructions should be followed by everyone. Fortunately, more than 95% of COVID-19 patients experience mild symptoms and can be taken care of at their residence (home quarantined). Glycated hemoglobin (HA1c) levels are significantly high in type I diabetes. As a result, the patient becomes highly susceptible to infections in an immunocompromised environment. Studies have shown severe ketoacidosis in type I diabetic patients with COVID-19. Regular monitoring of blood sugar and ketone levels along with proper awareness about the disease and its implications during infections is absolutely vital. Regular and appropriate doses of insulin should be administered [22]. Dehydration should be avoided, and energy levels maintained.

There are no approved therapies for COVID-19 and hence the focus is more on prevention and repurposing already available drugs that may be effective against this virus. In case of SARS-CoV-2 infecting diabetic patients, insulin administration is preferred for getting hyperglycemia under control. Oral drug administration, particularly metformin and sodium glucose cotransporter-2 in-

hibitors, have been advised to be discontinued [23]. There are several reports where usage of drugs like lopinavir, ritonavir, interferon β-1b, RNA polymerase inhibitor remdesivir, and chloroquine have been advised although their efficacy is still doubtful and not confirmed [24]. SARS-CoV-2 has receptors that strongly bind to ACE2 and hence, as discussed earlier, RAS inhibition may play a role in the treatment of severe respiratory diseases [25] [26]. There are some antivirals that show promising effects against other viruses. Zinc nanoparticles have been shown to inhibit H1N1 but have not been tested against SARS-CoV-2 [27]. Similarly, Vitamin C, which showed a positive effect in the prevention of pneumonia, should be evaluated against COVID-19 [28]. Dexamethasone, a corticosteroid used for the treatment of many conditions like asthma, allergies etc, has been recommended for use in COVID-19 patients by WHO and many health organisations. Caution must be taken in using it against diabetic patients as this anti-inflammatory drug may increase blood glucose levels [29].

Metformin is a widely prescribed drug that lowers blood sugar levels in type 2 diabetes patients. It is also prescribed to those who have risk of developing this metabolic disorder due to obesity and other conditions. Metformin stimulates AMPK pathway. It has been reported that AMPK increases the expression of phosphorylated ACE-2 Ser[680] in HEK293T cells. Addition of a phosphate group leads to conformational changes in ACE-2 receptor and prevents its activation. Also, it inhibits mTOR via liver kinase B1 pathway which plays an important role in MERS-CoV infection. It is hypothesised that metformin affects this pathway in SARS-CoV-2 infection, but more data is needed to confirm this [30] [31] [32]. Some reports interestingly claim that metformin has the ability to reduce inflammatory response and may help in reducing mortality rates [30] [33]. In the absence of any specific treatment or vaccine, these drugs should be used but only after careful analysis of their effect on both the virus and host. [34]. Miglitol, celgosivir and miglustat are some drugs that need to be evaluated as treatment options against COVID-19 [35]. Table 1 is a compilation of commonly used antidiabetic drugs and their effect, if any, on COVID-19. Research is also going on to use the spike proteins of SARS-CoV-2 as potential candidates for the development of vaccines. Antibodies generated against these proteins, isolated from patients after recovery are used as a treatment option. Vaccines play a major role in containing the pandemic. Their development is in progress and till then we have to depend on available drugs and various treatment strategies.

2. Conclusion

The health systems of several countries are hard-pressed due to the COVID-19 pandemic. The continuous lockdowns and social distancing measures have destroyed quite a few economies across the world. People are waiting with hope for normalcy to return which is unlikely until effective antiviral drugs and vaccines are available. In the current situation when there is no approved drug or vaccine

Table 1. Commonly used antidiabetic drugs and their effect on COVID-19.

Diabetes type	Drug Class	Drugs	Mode of action	Side effects	Antiviral activity	References
Type 1 Diabetes	Insulin	Humulin Novolog Tresiba	Restoration and maintenance of β-cell function	Hypoglycemia, weight gain	No direct effect reported on ACE-2	[36] [37]
	Amylinomimetic drug	Pramlintide	Synthetic analogue of amylin, helps in regulation of blood glucose and inhibits glucagon secretion	Nausea, anorexia, abdominal pain, hypoglycemia, headache,	No data currently available on their effect COVID-19 patients	[38]
Type 2 Diabetes	α-glucosidase inhibitors	Acarbose Miglitol	competitive inhibitor of α-glucosidase enzyme which hydrolyzes complex sugars into glucose in the small intestine	Diarrhea, hypoglycemia	Disrupt SARS-CoV-2 probably by interfering with S-protein folding mechanisms like N-glycosylation and calnexin pathway; may also effect ACE-2 and membrane fusion between host-virus endosomes	[39] [35] [40]
	Biguanides	Metformin (Glucophage, Metformin Hydrochloride ER, Glumetza, Riomet, Fortamet)	Reduce glucose formation in the liver, inhibit mitochondrial repiration, stimulate AMP-activated protein kinase and decreasegluconeogenesis	Gastric problems, vomiting, nausea, weakness, metallic taste in mouth may occur	Stimulation of AMPK pathway and addition of a phosphate group leads to conformational changes and deactivation of ACE-2 receptors. Also inhibits mTOR via liver kinase B1 pathway crucial to SARS-CoV-2 infection.	[30] [31] [41] [42] [43] [44] [45]
	Dopamine agonists	Bromocriptine (Cycloset)	lower HbA1c, act mainly on glucose/lipid metabolism and central nervous system	Dizziness, nausea	No data currently available on their effect COVID-19 patients	[46]
	Dipeptidyl peptidase-4 (DPP-4) Inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin	inhibit activity of DPP-4, an enzyme which destroys incretins, hormones that stimulate decrease in blood glucose levels	Respiratory infections, headache	Reduce entry and replication of the virus, inhibit ACE and reduce angiotensin-II, diminish cytokine secretion and reduce inflammatory markers in lungs of COVID-19 patients.	[47] [48] [49] [50]
	Glucagon like peptide-1 receptor agonists (GLP-1 receptor agonists)	Albiglutide Dulaglutide Exenatide Liraglutide Semglutide	mimicincretin and activate GLP-1 receptor	Nausea, vomiting	Suggested that they increase expression of ACE2 receptors but no evidence to date	[51] [52]
	Meglitinides	Nateglinide Repaglinide	bind to SUR1 receptor on β-cell and stimulate insulin secretion	Weight gain, hypoglycemia	No data currently available on their effect COVID-19 patients	[53]

Continued

	Sodium-glucose transporters (SGLT) 2 inhibitors	Dapagliflozin Canagliflozin Empagliflozin Ertugliflozin	Suppress SGLT-2, reduce glucose absorption in renal tubules and ultimately reduce blood glucose levels	Uro-gential tract infection, abdominal pain, nausea	Studies suggest they reduce inflammatory response, macrophage IL-1β and TNF-α in patients	[54] [55]
	Sulfonylureas	Glimepiride Gliclazide Glyburide Chlorpropamide Tolazamide Tolbutamide	Stimulate insulin from β-cells by closing of potassium channels and opening of calcium channels.	Weight gain, headache, hypoglycemia	No data currently available on their effect COVID-19 patients	[56]
	Thiazolidinediones (TZD)	Rosiglitazone Pioglitazone	activate the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and stimulates the transcription of the genes involved in the management of high glucose levels	Edema, weight gain, hypoglycemia	Studies suggested that Pioglitazone reduces the inflammatory markers like TNF-α, IL-6, elevated C-reactive levels in COVID-19 patients. Also some data suggested that TZD pioglitazone increases ACE-2 levels	[57] [58] [59] [60]
Gestational Diabetes	Biguanides, Insulin, Sulfonylureas etc.	Metformin Insulin, etc	Lowering glucose levels	Obesity	Upregulation of ACE-2 contributes to more sensitivity against SARS-CoV-2	[61]

against COVID-19, it is convenient to repurpose already approved drugs or drugs undergoing clinical trials. The mechanism of action, and antiviral targets need to be further evaluated. Patients with co-morbidities like diabetes are definitely at higher risk and hence need special attention. Thus, it is imperative that people with diabetes mellitus take all necessary precautions and ensure good glycemic control amid the ongoing pandemic. Further studies are required that will help in the development of effective vaccines to completely eradicate these pathogens.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] World Health Organization (2020) Novel Coronavirus-China. https://www.who.int/emergencies/diseases/novel-coronavirus-2019

[2] HealthMap (2020) Novel Coronavirus (COVID-19). https://www.healthmap.org/covid-19/

[3] Yang, J., Zheng, Y., Gou, X., Pu, K., Chen, Z.F., Guo, Q.H., *et al.* (2020) Prevalence of Comorbidities and Its Effects in Patients Infected with SARS-CoV-2: A Systematic Review and Meta-Analysis. *International Journal of Infectious Diseases*, **94**, 91-95. https://doi.org/10.1016/j.ijid.2020.03.017

[4]   Li, F. (2016) Structure, Function, and Evolution of Coronavirus Spike Proteins. *Annual Review of Virology*, **3**, 237-261. https://doi.org/10.1146/annurev-virology-110615-042301

[5]   Sah, R., Rodriguez-Morales, A.J., Jha, R., Daniel, K., Chu, W., *et al.* (2020) Complete Genome Sequence of a 2019 Novel Coronavirus (SARS-CoV-2) Strain Isolated in Nepal. *Microbiology Resource Announcements*, **9**, e00169-20. https://doi.org/10.1128/MRA.00169-20

[6]   Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., *et al.* (2020) Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation. *Science*, **367**, 1260-1263. https://doi.org/10.1126/science.abb2507

[7]   Zheng, J. (2020) SARS-CoV-2: An Emerging Coronavirus that Causes a Global Threat. *International Journal of Biological Sciences*, **16**, 1678-1685. https://doi.org/10.7150/ijbs.45053

[8]   Donoghue, M., Hsieh, F. and Baronas, E. (2000) A Novel Angiotensin-Converting Enzyme-Related Carboxypeptidase (ACE2) Converts Angiotensin I to Angiotensin 1-9. *Circulation Research*, **87**, E1-E9. https://doi.org/10.1161/01.RES.87.5.e1

[9]   Li, S.C., Wang, Z.J. and Yang, X.H., Hu, B., Huang, Y.L. and Fan, S.J. (2017) Association between Circulating Angiotensin-Converting Enzyme 2 and Cardiac Remodelling in Hypertensive Patients. *Peptides*, **90**, 63-68. https://doi.org/10.1016/j.peptides.2017.02.007

[10] Touyz, R.M., Li, H. and Delles, C. (2020) ACE2 the Janus-Faced Protein—From Cardiovascular Protection to Severe Acute Respiratory Syndrome-Coronavirus and COVID-19. *Clinical Science*, **134**, 747-750. https://doi.org/10.1042/CS20200363

[11] D'Amico, F., Baumgart, D.C., Danese, S. and Peyrin-Biroulet, L. (2020) Diarrhea during COVID-19 Infection: Pathogenesis, Epidemiology, Prevention, and Management. *Clinical Gastroenterology and Hepatology*, **18**, 1663-1672. https://doi.org/10.1016/j.cgh.2020.04.001

[12] Li, S.R., Tang, Z.J., Li, Z.H. and Liu, X. (2020) Searching Therapeutic Strategy of New Coronavirus Pneumonia from Angiotensin-Converting Enzyme 2: The Target of COVID-19 and SARS-CoV. *European Journal of Clinical Microbiology & Infectious Diseases*, **39**, 1021-1026. https://doi.org/10.1007/s10096-020-03883-y

[13] Liu, W.Z. and Li, H.L. (2020) COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. *ChemRxi*, Preprint. https://doi.org/10.26434/chemrxiv.11938173.v9

[14] Tang, N., Li, D. and Wang, X. (2020) Abnormal Coagulation Parameters Are Associated with Poor Prognosis in Patients with Novel Coronavirus Pneumonia. *Journal of Thrombosis and Haemostasis*, **18**, 844-847. https://doi.org/10.1111/jth.14768

[15] US Centres for Disease Control and Prevention (2020) National Diabetes Statistics Report. US Centres for Disease Control and Prevention, Atlanta. https://www.cdc.gov/diabetes/data/statistics-report/index.html

[16] Al Dawish, M.A., Robert, A.A., Braham, R., Al Hayek, A.A., Al Saeed, A. and Ahmed, R.A. (2016) Diabetes Mellitus in Saudi Arabia: A Review of the Recent Literature. *Current Diabetes Reviews*, **12**, 359-368. https://doi.org/10.2174/1573399811666150724095130

[17] International Diabetes Federation (2019) IDF Diabetes Atlas. 9th Edition. www.diabetesatlas.org

[18] Yang, J.K., Feng, Y., Yuan, M.Y., Yuan, S.Y., Fu, H.J., Wu, B.Y., Sun, G.Z., Yang, G.R., Zhang, X.L., Wang, L., Xu, X., Xu, X.P. and Chan, J.C.N. (2006) Plasma Glucose Levels and Diabetes Are Independent Predictors for Mortality and Morbidity

in Patients with SARS. *Diabetic Medicine*, **23**, 623-628.
https://doi.org/10.1111/j.1464-5491.2006.01861.x

[19] Schoen, K., Horvat, N., Guerreiro, N.F.C., de Castro, I. and de Giassi, K.S. (2019) Spectrum of Clinical and Radiographic Findings in Patients with Diagnosis of H1N1 and Correlation with Clinical Severity. *BMC Infectious Diseases*, **19**, Article No. 964. https://doi.org/10.1186/s12879-019-4592-0

[20] Pal, R. and Bhadada, S.K. (2020) COVID-19 and Diabetes Mellitus: An Unholy Interaction of Two Pandemics. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, **14**, 513-517. https://doi.org/10.1016/j.dsx.2020.04.049

[21] Dean, R.G. and Burrell, L.M. (2007) ACE2 and Diabetic Complications. *Current Pharmaceutical Design*, **13**, 2730-2735. https://doi.org/10.2174/138161207781662876

[22] Chowdhury, S. and Goswami, S. (2020) COVID-19 and Type 1 Diabetes: Dealing with the Difficult Duo. *International Journal of Diabetes in Developing Countries*, **40**, 315-320. https://doi.org/10.1007/s13410-020-00846-z

[23] Tikellis, C. and Thomas, M.C. (2012) Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. *International Journal of Peptide*, **2012**, Article ID: 256294.

[24] Hartmann-Boyce, J., Morris, E., Goyder, C., Kinton, J., Perring, J. and Nunan, D. (2020) Managing Diabetes during the COVID 19 Pandemic. https://www.cebm.net/covid-19/managing-diabetes-during-the-covid-19-pandemic/

[25] McKee, D.L., Sternberg, A., Stange, U., Laufer, S. and Naujokat, C. (2020) Candidate Drugs against SARS-CoV-2 and COVID-19. *Pharmacological Research*, **157**, Article ID: 104859. https://doi.org/10.1016/j.phrs.2020.104859

[26] Sun, M.L., Yang, J.M., Sun, Y.P. and Su, G.H. (2020) Inhibitors of RAS Might Be a Good Choice for the Therapy of COVID-19 Pneumonia. *Chinese Journal of Tuberculosis and Respiratory Diseases*, **43**, E014. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.0014

[27] Phadke, M. and Saunik, S. (2020) Use of Angiotensin Receptor Blockers Such as Telmisartan, Losartan in nCoV Wuhan Corona Virus Infections—Novel Mode of Treatment. *BMJ*, **368**, m406.

[28] Ghaffari, H., Tavakoli, A., Moradi, A., Tabarraei, A., Bokharaei-Salim, F., Zahmatkeshan, M., *et al.* (2019) Inhibition of H1N1 Influenza Virus Infection by Zinc Oxide Nanoparticles: Another Emerging Application of Nanomedicine. *Journal of Biomedical Science*, **26**, Article No. 70.

[29] Hemila, H. (1997) Vitamin C Intake and Susceptibility to Pneumonia. *The Pediatric Infectious Disease Journal*, **16**, 836-837.

[30] Hans, P., Vanthuyne, A., Dewandre, P.Y., Brichant, J.F. and Bonhomme, V. (2006) Blood Glucose Concentration Profile after 10 mg Dexamethasone in Non-Diabetic and Type 2 Diabetic Patients Undergoing Abdominal Surgery. *British Journal of Anaesthesia*, **97**, 164-170.

[31] Sharma, S., Ray, A. and Sadasivam, B. (2020) Metformin in COVID-19: A Possible Role beyond Diabetes. *Diabetes Research and Clinical Practice*, **164**, Article ID: 108183.

[32] Liu, J., Li, X., Lu, Q., Ren, D., Sun, X., Rousselle, T., *et al.* (2019) AMPK: A Balancer of the Renin-Angiotensin System. *Bioscience Reports*, **39**, Article ID: BSR20181994.

[33] Plattner, F. and Bibb, JA. (2012) Serine and Threonine Phosphorylation. In: Brady, S.T., Siegel, G.J., Wayne Albers, R. and Price, D.L., Eds., *Basic Neurochemistry*, 8th

Edition, Academic Press, Cambridge, 467-492.
https://doi.org/10.1016/B978-0-12-374947-5.00025-0

[34] Firstpost (2020) Metformin, an Oral Anti-Diabetic Drug, May Reduce Mortality in Women Infected by COVID-19, Claims Study.
https://www.firstpost.com/health/metformin-an-oral-anti-diabetic-drug-may-reduce-mortality-in-women-infected-by-covid-19-claims-study-8519791.html

[35] Gupta, R., Ghosh, A., Singh, A.K. and Misra, A. (2020) Clinical Considerations for Patients with Diabetes in Times of COVID-19 Epidemic. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, **14**, 211-212.
https://doi.org/10.1016/j.dsx.2020.03.002

[36] Williams, S.J., Goddard-Borger, E.D. (2020) α-Glucosidase Inhibitors as Host-Directed Antiviral Agents with Potential for the Treatment of COVID-19. *Biochemical Society Transactions*, **48**, 1287-1295. https://doi.org/10.1042/BST20200505

[37] Weng, J., Li, Y., Xu, W., Shi, L., Zhang, Q., Zhu, D. and Ran, X. (2008) Effect of Intensive Insulin Therapy on β-Cell Function and Glycaemic Control in Patients with Newly Diagnosed Type 2 Diabetes: A Multicentre Randomised Parallel-Group Trial. *The Lancet*, **371**, 1753-1760. https://doi.org/10.1016/S0140-6736(08)60762-X

[38] Swinnen, S.G., Hoekstra, J.B. and De Vries, J.H. (2009) Insulin Therapy for Type 2 Diabetes. *Diabetes Care*, **32**, S253-S259. https://doi.org/10.2337/dc09-S318

[39] Jones, M.C. (2007) Therapies for Diabetes: Pramlintide and Exenatide. *American Family Physician*, **75**, 1831-1835.

[40] Bischoff, H. (1995) The Mechanism of Alpha-Glucosidase Inhibition in the Management of Diabetes. *Clinical and Investigative Medicine*, **18**, 303-311.

[41] Ahidjo, B.A., Loe, M.W.C., Ng, Y.L., Mok, C.K. and Chu, J.J.H. (2020) Current Perspective of Antiviral Strategies against COVID-19. *ACS Infectious Diseases*, **10**, 1624-1634. https://doi.org/10.1021/acsinfecdis.0c00236

[42] Zhao, X., Guo, F., Comunale, M.A., Mehta, A., Sehgal, M., Jain, P. and Guo, J.T. (2015) Inhibition of Endoplasmic Reticulum-Resident Glucosidases Impairs Severe Acute Respiratory Syndrome Coronavirus and Human Coronavirus NL63 Spike Protein-Mediated Entry by Altering the Glycan Processing of Angiotensin I-Converting Enzyme 2. *Antimicrobial Agents and Chemotherapy*, **59**, 206-216.
https://doi.org/10.1128/AAC.03999-14

[43] Rena, G., Hardie, D.G. and Pearson, E.R. (2017) The Mechanisms of Action of Metformin. *Diabetologia*, **60**, 1577-1585. https://doi.org/10.1007/s00125-017-4342-z

[44] Kirpichnikov, D., McFarlane, S.I. and Sowers, J.R. (2002) Metformin: An Update. *Annals of Internal Medicine*, **137**, 25-33.
https://doi.org/10.7326/0003-4819-137-1-200207020-00009

[45] Nasri, H. and Rafieian-Kopaei, M. (2014) Metformin: Current Knowledge. *Journal of Research in Medical Sciences*, **19**, 658-664.

[46] Clements, A., Gao, B., Yeap, S.H.O., Wong, M.K.Y., Ali, S.S. and Gurney, H. (2011) Metformin in Prostate Cancer: Two for the Price of One. *Annals of Oncology*, **22**, 2556-2560. https://doi.org/10.1093/annonc/mdr037

[47] Kindrachuk, J., Ork, B., Hart, B.J., Mazur, S., Holbrook, M.R., Frieman, M.B. and Olinger, G.G. (2015) Antiviral Potential of ERK/MAPK and PI3K/AKT/mTOR Signaling Modulation for Middle East Respiratory Syndrome Coronavirus Infection as Identified by Temporal Kinome Analysis. *Antimicrobial Agents and Chemotherapy*, **59**, 1088-1099. https://doi.org/10.1128/AAC.03659-14

[48] Lamos, E.M., Levitt, D.L. and Munir, K.M. (2016) A Review of Dopamine Agonist Therapy in Type 2 Diabetes and Effects on Cardio-Metabolic Parameters. *Primary

Care Diabetes, **10**, 60-65. https://doi.org/10.1016/j.pcd.2015.10.008

[49] Thornberry, N.A. and Gallwitz, B. (2009) Mechanism of Action of Inhibitors of Dipeptidyl-Peptidase-4 (DPP-4). *Best Practice & Research Clinical Endocrinology & Metabolism*, **23**, 479-486. https://doi.org/10.1016/j.beem.2009.03.004

[50] Pathak, R. and Bridgeman, M.B. (2010) Dipeptidyl-Peptidase-4 (DPP-4) Inhibitors in the Management of Diabetes. *Pharmacy and Therapeutics*, **35**, 509-513.

[51] Abouelkheir, M. and El-Metwally, T.H. (2019) Dipeptidyl Peptidase-4 Inhibitors Can Inhibit Angiotensin Converting Enzyme. *European Journal of Pharmacology*, **862**, Article ID: 172638. https://doi.org/10.1016/j.ejphar.2019.172638

[52] Solerte, S.B., Di Sabatino, A., Galli, M. and Fiorina, P. (2020) Dipeptidyl Peptidase-4 (DPP4) Inhibition in COVID-19. *Acta Diabetologica*, **57**, 779-783.

[53] Meier, J.J. (2012) GLP-1 Receptor Agonists for Individualized Treatment of Type 2 Diabetes Mellitus. *Nature Reviews Endocrinology*, **8**, 728-742.

[54] Ceriello, A., Standl, E., Catrinoiu, D., Itzhak, B., Lalic, N.M., Rahelic, D. and Valensi, P. (2020) Issues of Cardiovascular Risk Management in People with Diabetes in the COVID-19 Era. *Diabetes Care*, **43**, 1427-1432. https://doi.org/10.2337/dc20-0941

[55] Guardado-Mendoza, R., Prioletta, A., Jiménez-Ceja, L.M., Sosale, A. and Folli, F. (2013) The Role of Nateglinide and Repaglinide, Derivatives of Meglitinide, in the Treatment of Type 2 Diabetes Mellitus. *Archives of Medical Science*, **9**, 936-943. https://doi.org/10.5114/aoms.2013.34991

[56] Kalra, S. (2014) Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors: A Review of Their Basic and Clinical Pharmacology. *Diabetes Therapy*, **5**, 355-366. https://doi.org/10.1007/s13300-014-0089-4

[57] Soni, S. and Dyck, J.R. (2020) The Multiple Effects of SGLT2 Inhibitors Suggest Potential Benefit in COVID-19 Patients. *Canadian Journal of Cardiology*, **36**, 1691.e3. https://doi.org/10.1016/j.cjca.2020.07.230

[58] Rendell, M. (2004) The Role of Sulphonylureas in the Management of Type 2 Diabetes Mellitus. *Drugs*, **64**, 1339-1358. https://doi.org/10.2165/00003495-200464120-00006

[59] Kahn, C.R., Chen, L. and Cohen, S.E. (2000) Unravelling the Mechanism of Action of Thiazolidinediones. *The Journal of Clinical Investigation*, **106**, 1305-1307. https://doi.org/10.2165/00003495-200464120-00006

[60] Carboni, E., Carta, A.R. and Carboni, E. (2020) Can Pioglitazone Be Potentially Useful Therapeutically in Treating Patients with Covid-19? *Medical Hypotheses*, **140**, Article ID: 109776. https://doi.org/10.1016/j.mehy.2020.109776

[61] Zhang, W., Xu, Y.Z., Liu, B., Wu, R., Yang, Y.Y., Xiao, X.Q. and Zhang, X. (2014) Pioglitazone Upregulates Angiotensin Converting Enzyme 2 Expression in Insulin-Sensitive Tissues in Rats with High-Fat Diet-Induced Nonalcoholic Steatohepatitis. *The Scientific World Journal*, **2014**, Article ID: 603409. https://doi.org/10.1155/2014/603409