Content available at: <https://www.ipinnovative.com/open-access-journals>

International Journal of Clinical Biochemistry and Research

Journal homepage: <https://www.ijcbr.in/>

Review Article

Progression of knowledge in diabetes mellitus and covid-19

VL Asha Latha^{1,*}¹Dept. of Biochemistry, Mahavir Institute of Medical Sciences, Vikarabad, Telangana, India

ARTICLE INFO

Article history:

Received 05-07-2021

Accepted 02-09-2021

Available online 08-10-2021

Keywords:

Angiotensin converting enzyme 2

Corona virus disease

Diabetes mellitus

Hyperglycemia

Pathophysiology

SARS CoV 2

ABSTRACT

The Coronavirus Disease 19 (COVID-19) is a pandemic infectious disease caused by the novel corona virus Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). Diabetes mellitus (DM) and hyperglycemia are among the major comorbidities in patients with COVID-19 which might modulate immune and inflammatory responses leading to poor outcomes. Several reports show that patients with DM and COVID-19 are at an increased risk for developing severe complications including acute respiratory distress syndrome, multi-organ failure, and death. Furthermore, compromised innate immunity, pro-inflammatory cytokine milieu, reduced expression of ACE-2 and use of renin-angiotensin-aldosterone system antagonists in diabetic patients may also contribute to poor prognosis in COVID-19. However, the mechanisms underlying the relationship between COVID-19 and DM remain to be elucidated. The severity and mortality was significantly higher in diabetic patients which may predispose patients with COVID-19 to poor outcomes. Most of these conclusions are preliminary, and further investigation of the optimal management in diabetic patients is necessary. Thus, it is imperative that diabetic patients should take all necessary precautions and ensure good glycemic control amid with COVID-19 pandemic.

This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](#), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprint@ipinnovative.com

1. Introduction

The Corona Virus Disease 19 (COVID-19) is an infectious disease caused by a novel corona virus, the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), was declared as global pandemic by the World Health Organization (WHO) on March 11, 2020.¹ Although SARS-CoV-2 has shown phylogenetic and clinical similarities with SARS-CoV, the novel corona virus has higher transmissibility and lower case fatality rates.² In spite of low mortality rate of COVID-19, patients with co-morbidities such as hypertension, cardiovascular disease (CVD), obesity and diabetes mellitus (DM) are prone to more severe symptoms leads to increase in mortality.^{3,4}

DM is a chronic metabolic disorder that currently affects about 422 million persons worldwide^{5,6} and several

evidences^{7,8} has highlighted that DM is one of the major risk factors for fatal outcomes from COVID-19. It is known that diabetic patients are vulnerable to infection because of hyperglycemia in which angiotensin converting enzyme 2 (ACE2) is a receptor for SARS-CoV-2 in the human body leading to impaired immune function.⁹ COVID-19 and DM both are associated with acute and chronic inflammation, which can impact each other in the clinical progression and outcome. Therefore, it is vital to review studies on the effect of these diseases and the pharmacological approach in the management of diabetes coexisting with COVID-19. In addition, knowledge of the molecular mechanism of viral entry and replication can direct the treatment strategies and future research on targeted antiviral drugs and vaccines. In this review, we describe potential mechanisms underlying the increased susceptibility of diabetic patients to more COVID-19 disease, and also summarize the

* Corresponding author.

E-mail address: vlashalatha@gmail.com (V. L. A. Latha).

basic knowledge which extends the focus towards clinical recommendations for diabetic patients at risk of or affected by COVID-19.

2. Materials and Methods

An unrestricted search to December 31, 2020 in Scopus, PubMed, Science direct, Google Scholar databases and Web of science was executed. We searched the articles related to “Type 1 diabetes mellitus”, “Type 2 diabetes mellitus”, “new onset diabetes”, “pathophysiology”, “age”, “gender”, “hyperglycaemia”, “comorbidities”, “hypertension”, “cardiovascular disease”, “obesity”, in conjunction with the terms “COVID-19” and “SARS-CoV-2”. In addition, reference lists of eligible articles were screened for further relevant studies and systematic reviews scanned for appropriate references. No criteria for publication data were set, and all articles in English were included if published before August 30, 2020.

2.1. Clinical features

The COVID-19 is a highly contagious disease which showed the wide spectrum of clinical presentations ranging from asymptomatic infection to severe disease and classified based on the severity¹⁰ i.e. into mild, moderate, severe, and critical forms.³ The most common symptoms are fever (98.6%), fatigue (69.6%), dry cough, and diarrhoea, myalgia, and dyspnoea and uncommon symptoms include sputum production, headache, haemoptysis, and diarrhoea.

The severity of COVID-19 in mild patients (81%) had non-pneumonia or mild pneumonia with symptoms of an upper respiratory tract viral infection¹¹ i.e. dry cough, mild fever, nasal congestion, sore throat, headache, muscle pain, and malaise. Those with severe disease present with severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, or septic shock¹¹ with clinical findings i.e. severe dyspnea, tachypnea (respiratory rate > 30/minute), respiratory distress, SpO₂ ≤ 93%, PaO₂/FiO₂ < 300, and/or greater than 50% lung infiltrates within 24 to 48 hours. Critical patients had severe conditions, such as respiratory failure, septic shock, and/or multiple organ dysfunction or failure.¹¹

Data from the Chinese Centres for Disease Control and Prevention (CDC) suggest that the case fatality rate for critical patients is 49%¹¹ and patients without comorbidities have a lower case fatality rate (0.9%). Patients with pre-existing comorbidities have a higher case fatality rate, which include DM (7.3%), respiratory disease (6.5%), cardiovascular disease (CVD) (10.5%), hypertension (6%), and oncological complications (5.6%).¹²

2.2. Diagnosis

Understanding the evolving of COVID-19, the interim guidance has been issued by the WebPages with links

and World Health Organization (WHO), by the United States Centres for Disease Control and Prevention (US CDC), Europe Centre of Disease Control (CDC), US FDA.

The preliminary identification of the SARS-CoV-2 has been conducted by viral research institution in China through the classical Koch's postulates and observing its morphology through electron microscopy.¹³ The clinical diagnosis of SARS-CoV-2 is mainly based on a history of epidemiology, clinical manifestations and some additional examinations, such as detection of nucleic acids, CT scans, IgM/IgG immune identification technology (POCT), related to enzymes, immunosorbent assay (ELISA) and blood culture.¹⁴

So far, the golden clinical diagnosis method of COVID-19 is nucleic acid detection in the nasal and throat swab sampling or other respiratory tract samplings by real-time PCR (RT-PCR), chest x-ray or CT scan and further confirmed by next-generation sequencing. The primers for the SARS-CoV were developed with onset of disease in 2003 and are available on the WHO website at www.who.int/csr/sars/primers. Presently ready to use PCR kits are available for detections of this virus from various specimens. Furthermore, clinical symptoms as well as indications of patients infected with SARS-CoV-2 are very unusual, such as respiratory symptoms, coughing, fever, dyspnea, and viral pneumonia. Furthermore, additional tests are needed for the diagnosis of COVID-19, as well as epidemiological history of the patients.

2.3. Transmission

The early major cases (55%) clustered in Wuhan were linked to the direct contact with local seafood whole sale market and from local residents, but very soon WHO identified that human-to-human is the frequent spread mode of transmission.¹⁵ SARS-CoV-2 like SARS virus binds to the human angiotensin-converting enzyme 2 receptor (ACE-2) located on type II alveolar and intestinal cells.¹³ Thus major mode of transmission of COVID-19 is inhalation of infectious aerosols which include direct inhalation of contaminated droplets released into the environment by sneezing or coughing, and contact transmission via oral, nasal, and eye mucous. Microbes in droplets <5 μm in diameter can stay in the air for a long time and can be transmitted to others over distances of more than 1m. The transmission ways of COVID-19 in humans were proposed with incubation time of 2-14 days.¹⁶ In lab experiments, infectious SARS-CoV particles were detected in aerosols for 3 hrs.¹⁷ Some studies have shown the presence of asymptomatic viral carriers with normal laboratory and chest CT findings.^{18,19} The relative mechanism of asymptomatic carriers to the COVID-19 disease burden remains unclear so an effective intervention is needed to prevent and control the spread of COVID-19.

2.4. Clinical management

COVID-19 in majority of the population (80%) presents as an asymptomatic or mild infection however, the pneumonia and multiple complications, especially in certain high-risk groups are developed by the disease. This can be achieved with the use of acetaminophen, external cooling, oxygen therapy, nutritional supplements, and anti-bacterial therapy. The remaining 20% of infected patients will need admission and hospital care, including 5% of them requires high flow oxygen, extracorporeal membrane oxygenation (ECMO), glucocorticoid therapy, and convalescent plasma therapy. Therapeutically, aerosol administration of alpha-interferon (5million units twice daily), chloroquine phosphate, and lopinavir/ritonavir and¹¹ other anti-virals like ribavirin and abidor¹² are suggested. The use of three or more anti-viral drugs simultaneously is not recommended. Ongoing clinical studies suggest that remdesivir (GS5734) can be used for prophylaxis and therapy.¹¹ Furthermore, a fusion inhibitor targeting the HR1 domain of spike protein is reported to have the potential to treat COVID-19. Most importantly, isolation remains the most effective measure for containment of COVID-19.

3. Association between COVID- 19 and DM

3.1. DM and COVID-19: General considerations and potential mechanisms

DM is one of the leading causes of morbidity and mortality worldwide, and it is remain to be rise over the next few decades and is more susceptible to broad range of infections and seems to be independently associated with COVID-19 severity.^{9,20–22} Many studies show that DM is a frequent pre-existing condition that is associated with severe disease and death in patients with COVID-19.²³ Furthermore, the prevalence of DM in patients with COVID-19 depends on the size and characteristics of study population. In a meta-analysis of 7 studies including 1576 patients from China, DM was the second most common comorbidity (9.7%) followed by hypertension.²²

The reports of the studies are suggested an association between DM and poor prognosis, increased mortality of COVID-19. So, to better understand COVID-19 in patients with DM both basically and clinically we must be aware of the clinical features, pathophysiology, and potential mechanisms that increase the risk is needed to provide better care and spur new investigations.

3.2. Covid-19, Hyperglycemia and ACE2

Several independent research groups investigated that both SARS-CoV as well as SARS- CoV-2 utilizes angiotensin converting enzyme-2 (ACE-2) as a cellular entry receptor.^{24,25} Several studies also suggests that ACE-2 protein is expressed in many human cells and tissues i.e.

alveolar cells of the lungs, pancreatic islets etc. and thus serves as the site of entry for the virus into the body.^{26–28}

Lu et al, suggests an association between ACE-2 and glucose regulation and found that ACE-2 knockout mice is more susceptible to high fat diet- induced pancreatic β -cell dysfunction than wild- type mice.²⁹ Furthermore, infection with SARS-CoV can cause hyperglycaemia in people without pre-existing diabetes mellitus. This finding and the localization of ACE-2 expression in the pancreas together suggest that corona viruses might specifically damages islets, potentially leading to hyperglycaemia.³⁰ SARS CoV-2 induced impaired ACE-2 activity may hypothetically attenuate the cardio protective role of ACE-2, exaggerate inflammation, and contribute to severe lung injury in COVID-19.

The primary target of SARS-CoV2 is lungs, in which hyperglycaemia leads to a rapid deterioration in spirometric functions, especially decreased forced expiratory volume in 1 second and forced vital capacity.³¹ Furthermore, the higher expression of “receptor” sites in pulmonary system could help to explain the great proneness in DM patients and hyperglycaemia for developing a severe disease.^{32,33} Further investigations are needed to better understand the role of ACE-2 in diabetic patients during SARS-CoV-2 infection, which would enable the development of better and more effective treatments for the COVID-19 pandemic. Studies using samples from patients with COVID-19 are warranted to investigate the co localization of SARS-CoV2 and ACE-2 and help in understanding the progression of COVID-19 and the viral pathogenesis of SARS- CoV2.

4. Hyperglycemia and COVID-19

Glycemic variability is a prognostic factor in diabetic patients with SARS-CoV2 infection. Bode et al.³⁴ reported that patients admitted with COVID-19 with either diabetes or uncontrolled hyperglycemia (defined by two blood glucoses of >180 mg/dL within a 24 hr period) had higher mortality and longer hospitalizations. The mortality rate was higher in those with uncontrolled hyperglycemia with or without known history of diabetes (41.7%) as compared to controlled diabetic patients (14.8%). Another recent study, among 7300 hospitalized patients with COVID-19 found that patients with diabetes and poorly controlled glycemia has higher death rate compared to patients with better controlled blood glucose.⁹

Several pathophysiological mechanisms were put forward in supporting the association between DM and COVID-19 severity. Some of them are higher-affinity cellular binding, efficient viral entry, reduced viral clearance, reduced T-cell function, enhanced susceptibility to hyper inflammation and cytokine storm, and the presence of cardiovascular diseases.³⁵ The COVID-19 infection forces the stress of DM by releasing glucocorticoids and catecholamines into circulation. These worsen glycemic

control and increase the formation of glycation end products in many organs and worsen prognosis.⁵ In addition, hyperglycemia worsens the outcome by the process of cytokine storm, endothelial dysfunction, and multiple organ injuries.³⁶

Apart from worsening of hyperglycemia, a retrospective study from Wuhan reported that around 10% of the patients with DM and COVID-19 suffered at least one episode of hypoglycaemia (<3.9 mmol/L).³⁷ Hypoglycemia, in turn, contributes to cardiovascular events in patients with DM by undue activation of the sympathetic nervous system and by mobilizing pro-inflammatory monocytes and enhancing platelet aggregation.³⁸ Rodriguez-Gueterrez R et al³⁹ found that severe hypoglycemia which may occur with strict glycemic control may worsen the overall mortality rate.

4.1. SARS-CoV2 link with DM, immunity, cytokines and increased inflammation

Innate immune system, the first line of defence against SARS-CoV-2, is compromised in patients with uncontrolled DM.⁵ The immune dysfunction in DM is contributed by several factors, including hyperglycemia, inhibition of neutrophil chemotaxis, altered cytokine production, phagocytic cell dysfunction, impaired T cell-mediated immune responses, and ineffective microbial clearance.⁴⁰

The onset and progression of SARS-CoV-2 infection is favoured in DM, by enhancing the inflammatory reaction of innate immune system and impairing the adaptive immune response to the virus.⁴¹ The humoral system, which mediates immediate defence responses by polymorphs, macrophages and dendritic antigen presenting cells to pathogens, is attenuated in DM.⁴² Therefore, increased susceptibility to infections has been related to several immune defects, i.e. blunted anti-viral interferon- γ response, delayed activation of CD4+ cells with shift toward Th17 responses, and diminished regulatory T cells, which all contribute to hyper inflammation.^{35,43} Furthermore, increased production of advanced glycation end products may also inhibit the generation of γ -interferon by T lymphocytes⁴⁴ which could reduce antiviral activity and increase the severity of infection.

Yan Y⁸ and his colleagues observed that immune, inflammatory and coagulation abnormalities are significantly pronounced in diabetics than in non-diabetics in patients with COVID-19, independently of other co morbidities, and to correlate with glycemic control,⁴⁵ which may suggest that they are responsible for the exacerbating effect of diabetes with related co-morbidities. Evidence has suggested that SARS-CoV-2 infection associated with DM can trigger stress conditions with high secretion of hyperglycemic hormones (glucocorticoid and catecholamines) which results in insulin resistance, hyperglycemia and other complications.^{46,47} The main target for infection is the insulin producing pancreatic

β -cells in the body leading to the subsequent destruction, thus worsening the glucose homeostasis.

Respiratory viral infections including SARS-CoV-2 generates the production of increased levels of mainly type-1 cytokines, including interleukins (ILs), IL-1, IL-8, chemokines, interferon (IFN- γ), interferon-gamma-inducible protein-10 (IP-10), monocyte chemotactic protein-1 (MCP-1) and tumor necrosis factor (TNF) in the blood which is named as cytokine storm.⁴⁸ The concentration of these cytokines can be a predictive factor in disease course and outcome,⁴⁹ investigations on the influence of the interaction between comorbidities, COVID-19 and cytokines in DM are crucial for the development of new treatments for COVID-19.⁵⁰

Several studies have enumerated that serum levels of interleukin-6 (IL-6), C-reactive protein (CRP) and ferritin were significantly higher in patients with DM than those without DM which is depicted in COVID-19 patients.^{51–53}

As already discussed, the up regulation of ACE-2 is associated with an increase in the levels of IL-1, IL-10, IL-6, and IL-8 which are important cytokines in the pathophysiology of COVID-19.^{4,54} However, IL-10 that acts as a negative regulator of inflammation process which is at lower levels in diabetic patients.⁵⁵ Fewer studies have highlighted the usage of anti-TNF and anti-IL-1 β to regulate inflammation in COVID-19 patients.⁵⁶ Thus, it is critical to maintain a balance between pro and anti-inflammatory mechanisms to have balanced lung homeostasis. This finding put forwards that diabetic patients are more susceptible to an inflammatory cytokine storm eventually leading to acute respiratory distress syndrome (ARDS), shock and rapid deterioration of COVID-19.

In this review, we detail our present understanding of the pathogenesis of SARS-CoV-2 and elucidate possible mechanisms behind the increased susceptibility of DM patients to infections.

4.2. Medical management of DM and COVID-19

Uncontrolled or stress hyperglycemia is associated with increased severity of COVID-19 and mortality. In addition, a very high level of blood glucose advances in the patient's illness and reaches to severe levels.^{57,58} Hyperglycemia can also induce glycation of ACE-2, which may cause increased entry of SARS-CoV-2 into the cells, leading to increased inflammation and hyper immune responses.⁵⁹ SARS-CoV-2 infection also increases the risk of thromboembolism which is likely to induce cardio respiratory failure in patients with DM than in patients without DM.^{60,61} All these mechanisms are contributed to the poor prognosis of patients with DM and COVID-19. Hence, it is essential to closely monitor and manage blood glucose levels in patients hospitalized with DM and COVID-19.

During the COVID-19 pandemic, the diabetic patients should be aware that COVID-19 can increase blood levels

of glucose and they should follow the clinical guidelines strictly for the management of DM. The diabetic patients should be extra vigilant in rigorous glucose monitoring and careful consideration to prescribed medications which may help in attenuating the worsening of symptoms and adverse clinical outcomes.^{4,54}

Even though hyperglycemia is main concern in this context, one should not ignore the hypoglycemic episodes as a result of viral pathogenesis, metabolic disturbances in DM and interplay between drug treatments. Based on the disease severity, presence of associated co morbidities and diabetes-related complications one should formulate the patient tailored therapeutic strategies and optimal glucose control goals. Thus, in order to elucidate the impact of DM as a risk factor for COVID-19 and to explore the best prophylactic and therapeutic strategies for this high-risk population, it is critical to design and conduct high-quality, robust observational studies and clinical trials.

5. Conclusion

The knowledge about COVID-19 is growing rapidly in which DM is most frequently reported co morbidities in patients infected with COVID-19. There is paucity of data in the India regarding comorbidities associated with DM and COVID-19 outcomes and mechanisms that modulate viral pathogenesis. Therefore it is pivotal for clinicians to care for COVID-19 and diabetic patients in sense of metabolic risk factors associated with severity of disease, and the developments emerging on the metabolic interactions between anti-diabetic agents, RAAS inhibitors and potential drug treatments.

Identification of clinical and biochemical parameters using multi-omics approaches that predict severity of the COVID-19 in DM using large data sets is urgently needed. The great challenge in management of diabetes in COVID-19 patients is required by much-integrated therapy which is an indispensable strategy to reduce the risk of medical complications of the disease. Careful assessment of many components that contribute to poor prognosis with COVID-19 in diabetic patients may represent the best to overcome the current situation and enable our health systems to face any future challenges in a prompt and effective management.

6. Conflicts of Interest

None.

Acknowledgements

I thank to my parent Dept. of Biochemistry of Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati for constantly guiding and inspiring me.

References

1. Open database: WHO certified [database on the Internet] (2020b)
2. Coronavirus disease 2019 (COVID-19) situation report-36. Available from: <http://www.who.int>.
3. Ceccarelli M, Berretta M, Rullo EV, Nunnari G, Cacopardo B. Differences and similarities between Severe Acute Respiratory Syndrome (SARS)-Corona Virus (CoV) and SARS-CoV-2. Would a rose by another name smell as sweet? *Eur Rev Med Pharmacol Sci*. 2020;24(5):2781–3.
4. Wu Z, Mcgoogan JM. Characteristics of and important lessons from the corona virus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239–42.
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–20.
6. Ugwueze CV, Ezeokpo BC, Nnolim BI, Agim EA, Anikpo NC, Onyekachi KE. COVID-19 and Diabetes Mellitus: The Link and Clinical Implications. *Dubai Diabetes Endocrinol J*. 2020;26(2):69–77.
7. WHO Director-General's opening remarks at the media briefing on COVID-19. Available from: <http://www.who.int>.
8. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020;31:e3319.
9. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of severe COVID-19 patients with diabetes. *BMJ Open Diab Res Care*. 2020;8:e001343.
10. Zhu L, She ZG, Xu C, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab*. 2020;31(6):1068–77.
11. Shishir P, Ganesh D, C A, Ram T, Ojash B, D. The Coronavirus Pandemic: What Does the Evidence Show? *J Nepal Health Res Counc*. 2020;18(46):1–9.
12. Cascella M, Rajnik M, Aleem A, Scott C, Dulebohn, Napoli RD. Features, Evaluation and Treatment Coronavirus (COVID-19). Treasure Island: Stat Pearls Publishing; 2020.
13. Yixuan W, Yuvi W, Chen Y, Qingsong Q. Unique epidemiological and clinical features of the emerging 2019 novel corona virus pneumonia (COVID-19) implicate special control measures. *J Med Virol*. 2020;92(6):568–76.
14. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. *J Med Virol*. 2020;92(4):401–2.
15. Guo YR, Cao QD, Hong ZS, Tan Y, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak-an update on the status. *Mil Med Res*. 2020;7:1.
16. Ye Q, Wang B, Mao J, Fu J, Shang S, Shu Q. Epidemiological analysis of COVID-19 and practical experience from China. *J Med Virol*. 2020;92(7):755–69.
17. Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV). *Euro Surveill*. 2020;25(4):2000058.
18. Doremalen NV, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med*. 2020;382(16):1564–7.
19. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen M. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. *J Microbiol Immunol Infect*. 2020;53(3):404–12.
20. Rahimi F, Abadi ATB. Challenges of managing the asymptomatic carriers of SARS-CoV-2. *Travel Med Infect Dis*. 2020;37:101677.
21. Holman N, Knighton P, Kar P, O'keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population- based cohort study. *Lancet Diabetes Endocrinol*. 2020;8(10):823–33.
22. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A. Baseline characteristics and outcomes of 1591 patients infected with SARS- CoV-2 admitted to ICUs of the Lombardy region. *JAMA*. 2020;323(16):1574–81.

22. Yang J, Zheng Y, Gou X, Ke P, Chen Z, Guo Q, et al. Prevalence of co morbidities and its effects in corona virus disease 2019 patients: a systematic review and meta-analysis. *Int J Infect Dis.* 2020;94:91–5.
23. Wang D, Hu B, Hu C, Zhu F, Liu X, Jing Z, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020;323(11):1061–9.
24. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271–80.
25. Ghebrawi M, Wang K, Viveiros A, Nguyen Q, Chang ZJ, Turner JA, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res.* 2020;126(100):1456–74.
26. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. *Viruses.* 2020;12(4):372.
27. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: an overview. *J Chi Med Assoc.* 2020;83(3):217–20.
28. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun.* 2020;109:102433.
29. Lu CL, Wang Y, Yuan L, Yang L, Li XY. The angiotensin-converting enzyme 2/angiotensin (1-7)/Mas axis protects the function of pancreatic β cells by improving the function of islet micro vascular endothelial cells. *Int J Mol Med.* 2014;34(5):1293–300.
30. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol.* 2010;47(3):193–9.
31. El-Azeem IAA, Hamdy G, Amin M, Rashad A. Pulmonary function changes in diabetic lung. *Egypt J Chest Dis.* 2013;62:513–17.
32. Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. *Nat Rev Endocrinol.* 2020;16(6):297–8.
33. Bindom SM, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. *Mol Cell Endocrinol.* 2009;302(2):193–202.
34. Bode B, Garrett V, Messler J, Mcfarland R, Crowe J, Booth R. Glycemic characteristics and clinical outcomes of COVID 19 patients hospitalized in the United States. *J Diabetes Sci Technol.* 2020;14(4):813–21.
35. Muniyappa R, Gubbi S. COVID-19 pandemic, corona viruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab.* 2020;318(5):736–41.
36. Constatino S, Paneni F, Battista R, Castello L, Capretti G, Chianotto S, et al. Impact of glycemic variability on chromatin remodeling, oxidative stress, and endothelial dysfunction in patients with type 2 diabetes and with target HbA1c. *Diabetes.* 2017;66(9):2472–82.
37. Zhou J, Tan J. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. *Metabolism.* 2020;107:154216. doi:10.1016/j.metabol.2020.154216.
38. Iqbal A, Prince LR, Novodvorsky P, Bernjak A, Thomas MR, Birch L, et al. Effect of hypoglycaemia on inflammatory responses and the response to low-dose endotoxemia in humans. *J Clin Endocrinol Metab.* 2019;104(4):1187–99.
39. Rodriguez-Gueterrez R, Gonzalez-Gonzalez JG, Zunga-Hernandez JA, McCoy RG. Benefits and harms of intensive glycemic control in patients with type 2 diabetes. *BMJ.* 2019;5887.
40. Hotamisligil GS. Inflammation, meta inflammation and immune metabolic disorders. *Nature.* 2017;542(7460):177–85.
41. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr.* 2020;14(3):211–2.
42. Janeway CA, Medzhitov R. Innate immune recognition. *Annu Rev Immunol.* 2020;20:197–216.
43. Kreuzer D, Nikoospour E, Au B, Krougly O, Lee-Chan E, Summers KL. Reduced interferon- α production by dendritic cells in type 1 diabetes does not impair immunity to influenza virus. *Clin Exp Immunol.* 2015;179(2):245–55.
44. Akirav EM, Henegariu O, Hurlburt PP, Schmidt AM, Clynes R, Herold KC. The receptor for advanced glycation end products (RAGE) affects T cell differentiation in OVA induced asthma. *PLoS One.* 2014;9(4):e95678.
45. Wang Z, Du Z, Zhu F. Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients. *Diabetes Res Clin Pract.* 2020;164:108214.
46. Odegaard JI, Chawla A. Connecting type 1 and type 2 diabetes through innate immunity. *Cold Spring Harb Perspect Med.* 2012;2(3):a007724.
47. Wang A, Zhao W, Xu Z, Gu J. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. *Diabetes Res Clin Pract.* 2020;162:108118.
48. Hassan N. Cytokine storm of SARS-CoV-2, the virus that causes COVID-19. *EJMED.* 2020;2(3):1–4.
49. Huang C, Wang Y, Li X, Ren L, Zhao J, Yi H, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497–506.
50. Pagliaro P, Penna C. A Key Also in 2019 Coronavirus Disease (Covid-19)? *Front Med (Lausanne).* 2020;7:335.
51. Rimesh P, Sanjay KB. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. *Diabetes Metab Syndr.* 2020;14(4):513–7.
52. Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. *Antivir Res.* 2020;178:104791.
53. Nakamura K, Kawasaki E, Imagawa A, Awata T, Ikegami H, Uchigata Y, et al. Type 1 diabetes and interferon therapy: a nationwide survey in Japan. *Diabetes Care.* 2011;34(9):2084–9.
54. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ. Clinical characteristics of 140 patients infected with SARSCoV-2 in Wuhan, China. *Allergy.* 2020;75(7):1730–41.
55. Kern L, Mittenbuhler MJ, Vesting AJ, Ostermann AL, Wunderlich CM, Wunderlich FT. Obesity induced TNF α and IL 6 signaling: The missing link between obesity and inflammation driven liver and colorectal cancers. *Cancers (Basel).* 2019;11(1):1–24.
56. Cauchois R, Koubia M, Delarbre D, Manet C, Carvellid J, Blasco VB, et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. *Proc Natl Acad Sci.* 2020;117(32):18951–3.
57. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Up regulation of angiotensin converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension.* 2004;43(5):970–6.
58. Ferrario CM, Jessup J, Chappell MC, Averil DB, Brosnihan KB, Tallant EA, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme. *Circulation.* 2005;111(20):2605–10.
59. Fosbøl L, Butt JH, Østergaard L, Andersson C, Selmer C, Kragholm K, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *JAMA.* 2020;324(2):168–77.
60. Chung WS, Lin CL, Kao CH. Diabetes increases the risk of deep-vein thrombosis and pulmonary embolism. A population-based cohort study. *Thromb Haemost.* 2015;114(4):812–8.
61. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood.* 2020;135(23):2033–40.

Author biography

VL Asha Latha, Associate Professor

Cite this article: Latha VLA. Progression of knowledge in diabetes mellitus and covid-19. *Int J Clin Biochem Res* 2021;8(3):163–168.