MINI REVIEW

Why Severity Rate of COVID-19 is High in Patients with Diabetes Mellitus: A Brief Insight

Romah Ishfaq[1], Anam Zulfiqar[2], Atif Zulfiqar[3], Asghar Javaid[4], Muhammad Zulfiqar[5], Naeem Akhtar[6]

ABSTRACT

Novel Coronavirus disease 2019 (nCOVID-19) a global pandemic is an ever-remaining threat for patients with Diabetic Mellites (DM). Herein, we have tried to provide brief insight to critically analyze the reasons causing the severity of Coronavirus disease (COVID-19) in patients diagnosed with DM. This, mini review highlights the key investigations starting from binding of COVID-19 at the cellular surface to create sever infection or even death in DM patients. The study further suggested to pay urgent attention towards stabilization of deadly immune response arises as a result of COVID-19. We hope the highlighted investigation will help the researchers to understand and develop a road map to deal DM patients infected with COVID-19 to minimize the severity rate.

KEYWORDS: COVID-19, Diabetic mellites, Infection, Severity.

How to Cite This:

Ishfaq R, Zulfiqar A, Zulfiqar A, Javaid A, Zulfiqar M, Akhtar N. Why severity rate of COVID-19 is high in patients with diabetes mellitus: A brief insight. Biomedica. 36 (COVID19-S2): 137-41.

Novel Coronavirus disease 2019 (nCOVID-19) that emerged in December 2019 is currently a global pandemic.[1] It is caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2).

1. Romah Ishfaq
Department of Pathology, Nishtar Medical University Multan-Pakistan.
2. Anam Zulfiqar
Department of Biochemistry
Baha-ud-Din Zakariya University, Multan-Pakistan.
3 Atif Zulfiqar
Department of Oral Surgery, Nishtar Institute of Dentistry, Multan-Pakistan.
4. Asghar Javaid
Department of Pathology, Nishtar Medical University, Multan-Pakistan.
5. Muhammad Zulfiqar
Principal Multan Dental College, MMDC Multan-Pakistan.
6. Naeem Akhtar
Interdisciplinary Research Centre in Biomedical Materials (IRCBM), COMSATS University Islamabad, Lahore -Pakistan.

Corresponding Author:
Dr. Naeem Akhtar
Assistant Professor
Interdisciplinary Research Centre in Biomedical Materials
COMSATS University Islamabad, Lahore Campus – Pakistan.
E-mail: naeemkhan@cuilahore.edu.pk

COVID-19 possess close resemblance with several bat Coronaviruses, thus reported as a new member of betaCoronavirus genus.[2] It exhibits more faster human-to-human transmission compared to previously reported SARS-CoV and Middle East Respiratory Syndrome–Coronavirus (MERS-CoV), which force the World Health Organization (WHO) to declare it a global emergency.[3] Although infections caused by Coronavirus are very mild compared to previous two outbreaks including SARS-CoV and MERS-CoV with mortality rate 10 and 36%, respectively.[4] However, mortality rate of all three outbreaks is almost same in individuals with diabetic mellitus (DM).

Unfortunately, more than 25% population of Pakistan is suffering from DM, according to the reported literature.[5] Thus, a wide population of Pakistan is at high risk for death fromCOVID-19. Additionally, wide range of asymptomatic individuals will remain a great threat to transmit the virus in future. Thus, it is of utmost importance to understand the reasons causing the severity of

COVID-19 in DM. Here in, we conducted a brief review, to provide critical assessment about severity of COVID-19 in DM patients by providing various reasons given by various researchers in their investigations. We hope this mini review can provide very useful information for future investigations and support in managing and controlling severity rate of COVID-19 in DM.

The literature used in this mini review is collected from PubMed and Google Scholar till May 19, 2020. The key words used during search include COVID-19, diabetes, infection, SARS-CoV-2. The most relevant literature was downloaded. We also got help from scientific literature and recommendations available in WHO website as well.

Brief Anatomical Features of COVID-19

It is very important to understand the anatomical features of COVID-19, before explaining the mechanisms or reasons involved in severity of COVID-19 in DM patients. The anatomical structure of COVID-19 (Fig.1) also provides fruitful information starting from contact with cellular structure to entry in cells as well. Basically, COVID-19 is made up of four different proteins including nucleocapsid (N), spike glycoprotein (S), membrane glycoprotein (M) and envelope protein (E).[6]

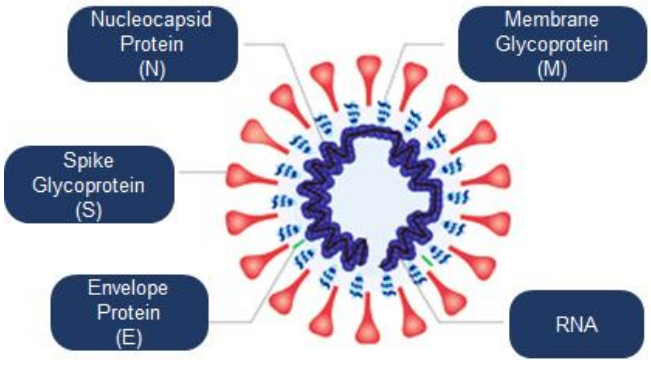

Fig.1: Anatomical structure of COVID-19 showing four different proteins including N, S, E and M. Figure is adopted and modified with the permission from reference.[7]

Increased Potential for Interaction with COVID-19

Angiotensin Converting Enzyme 2 (ACE-2) are attached on the outer surface cells of various organs including lungs, kidney, hearts, arteries and intestine.[8] The functionality of these ACE2 is to lower the blood pressure by converting angiotensin 2 (a vasoconstrictor) into angiotensin 1-7 (a vasodilator).[8] Unfortunately, these ACE-2 (**Fig. 2**) can also act as receptor for viruses such as COVID-19, influenzas etc.[9] On the other hand, patients with DM are recommended to use ACE inhibitor to control the nephropathy and cardiovascular diseases.[10] As a result of it, the level of ACE-2 receptor increase in DM patient, thus leading to increased affinity or maximize chances for viral attachment.

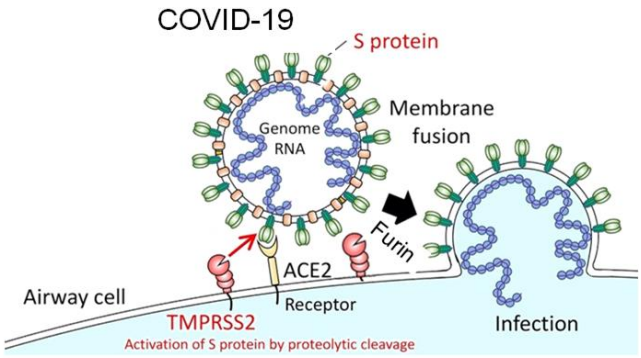

Fig.2: - Attachment of COVID-19 with ACE-2 receptor. Figure is adopted and modified with the permission from reference.[11]

Efficient Entry of COVID 19 in DM Patients

Once the virus is attached at the surface of cell via ACE-2, simultaneous increase in activation of multiple proteases such as Trans Membrane Serine Protease (TMPRSS2) and Furin is observed (Furin is a very important cellular protease and majorly involved in the development of metabolic syndromes such as DM.[12] However, the reason causing the development of DM *via* Furin is still unclear). The high content of activated Furin (**Fig. 2**) in DM patient, cleaves more spike structural protein of COVID-19, thus allowing its genome to enter more easily into the lung cells in the form of micro-vesicles.[11] The low pH

environment of cell along with cystine protease CATHEPSIN-L further support the release of genome from micro-vesicles.[13] As a result, the COVID-19 starts replicating by high-jacking the endogenies cellular machinery of host cell.

Diminished Immunological Response in DM

DM patients with elevated blood sugar (hyperglycemia) are immunosuppressed. Various mechanisms are involved behind this suppression. The brief details of theses mechanisms are as follows,

(i) Patients with chronic hyperglycemia may face acidosis, thus resulting in poor performance of immune system. Even though, acidosis and hyperglycemia could be treated but it leaves some adverse effects such as slow perfusion through blood vessels.[14]

(ii) DM patients with hyperglycemia have limited ability for neutrophil synthesis, thus leading to poor attacking ability on foreign objects.[15]

(iii) The level of cytosolic calcium in polymorphonuclear leukocytes (PMNs) increases in hyperglycemic patients.[16] This increased level of cytosolic calcium inhibits the synthesis of adenosine triphosphate (ATP), thus resulting in poor phagocytosis activity. Additionally, the mobilizing ability of PMN leukocytes to the site of infection and stimulation of apoptosis is also restricted.

(iv) Another reason behind the poor immune response in DM patients is low concentration of plasma zinc. In vitro studies suggested a disturbance in lymphocytic response and depression of chemotaxis as a result of low zinc concentration.[17]

Poor Viral Clearance in COVID-19 Patients

Here we explain the mechanisms in steps causing hindrance for viral clearance by immune cells.

Step 1. According to the reported literature, a DM patient have mismanaged glucose metabolic pathway. This poorly regulated metabolic pathway has direct impact on the synthesis of ATP and macrophage functionality.[18]

Step 2. Poor functionality of macrophages leads to reduced secretion of Interleukin 12(IL-12).[19]

Step 3. IL-12 is involved in the stimulation of natural killer cells and production of Interferon-γ (IFN-γ).

Step 4. IFN-γ major functionality is to protect against viral infection.[20] However, with poor or low production rate of IFN-γ leads to poor protective shield against viral attack.

Apart from all that, slow blood flow rate and hindered chemotaxis will also lead to very poor interaction of infected cells with immune cells. Moreover, cells with high glucose level are more prone to viral infection as evidenced from in vitro studies.

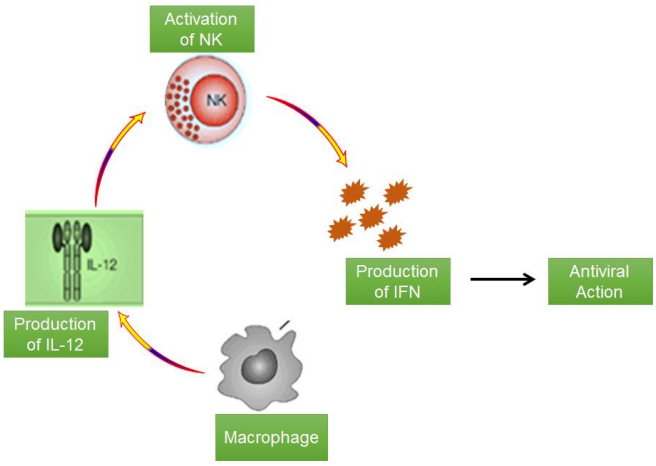

Fig.3: Schematic diagram showing mechanism of viral clearance.

Uncontrolled Cytokine Mediated Inflammation in Hyperglycemic COVID-19 Patients

It is surprising to mention that the concentration rate of people dying from COVID-19 is much lower than dying from their own immune response in case of DM patients.[21] Basically, a cytokine storm (a surge in cell-signaling proteins that prompt inflammation) is triggered as a result of infection.[22] This intense inflammation may lead to failure of various organs or tissues or even death. Such kind of immune response is also observed in some sever influenza cases as well.

Apart from trigging cytokine cells, synthesis of Advanced Glycosylation End Products (AGEs) and

oxidative stress level is also increase in hyperglycemia patients.[23]Basically, high level of blood glucose causes β-N-acetylglucosamine transferase (OGT) enzyme to bind and modify the Interferon Regulatory Factor 5 (IRF5) during glycosylation. This modification of IRF5 further leads to another chemical modification, called ubiquitination during which a protein is inactivated after attaching with ubiquitin.[24] As a Result the IRF5 is switched off and feedback mechanism of controlling the cytokine production is stopped. According to the reported literature, ubiquitination increases the chances for cytokine mediated uncontrolled inflammation, thus resulting in organ failure as well.

CONCLUSION

Even though COVID-19 has less mortality rate compared to SARS-CoV-2 and MERS-CoV but it is highly threatening for DM patients because of its fast-contagious ability. Several reasons causing the severity of COVID-19 in DM has been explained by various researchers. So here in, a brief but critical result of some reported literature has been highlighted. These highlights suggest that further research is urgently needed to clinically treat DM patients suffering from COVID-19 by maintaining their immune system.

LIMITATIONS OF STUDY

This is a short review based on selection of manuscripts without any formal protocol or guidelines. Hence the conclusions drawn may be inclined to selection bias.

ACKNOWLEDGMENT

The authors acknowledge Mrs. Rubina Zulfiqar for her support during write-up of this manuscript.

CONFLICT OF INTEREST

None to declare.

FINANCIAL DISCLOSURE

None to disclose.

REFERENCES

1. Zhao D, Yao F, Wang L, Zheng L, Gao Y, Ye J, et al. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias. Clin Infect Dis. 2020. [Epub ahead of print].
2. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of Coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020: 102433. [Epub ahead of print].
3. Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) Coronavirus 2019-nCoV infecting pregnant women: lessons from SARS, MERS, and other human Coronavirus infections. Viruses. 2020; 12 (2): 194-7.
4. Wang S, Guo L, Chen L, Liu W, Cao Y, Zhang J, et al. A case report of neonatal COVID-19 infection in China. Clin Infect Dis. 2020. [Epub ahead of print].
5. Zafar J, Nadeem D, Khan SA, Jawad MA, Aziz F, Saeed S. Prevalence of diabetes and its correlates in urban population of Pakistan: A Cross-sectional survey. J Pak Med Assoc. 2016; 66 (8): 922-7.
6. Schnell MJ, Buonocore L, Kretzschmar E, Johnson E, Rose JK. Foreign glycoproteins expressed from recombinant vesicular stomatitis viruses are incorporated efficiently into virus particles. Proc Natl Acad Sci.1996; 93 (21): 11359-65.
7. Guo YR, Cao QD, Hong ZS, Tan YY, 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): 1-10.
8. Fu J, Zhou B, Zhang L, Balaji KS, Wei C, Liu X, et al. Expressions and significance of the angiotensin-converting enzyme 2 gene, the receptor of SARS-CoV-2 for COVID-19. Mol Biol Reports. 2020: 84 (7): 1-10.
9. Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. EurResp J. 2020; 55 (5): 217-21.
10. Suissa S, Hutchinson T, Brophy J, Kezouh A. ACE-inhibitor use and the long-term risk of renal failure in diabetes. Kidney Int. 2006; 69 (5): 913-9.
11. Yamamoto M, Matsuyama S, Li X, Takeda M, Kawaguchi Y, Inoue J, et al. Identification of nafamostat as a potent inhibitor of Middle East Respiratory Syndrome Coronavirus S protein-mediated membrane fusion using the split-protein-based cell-cell fusion assay. Antimicrob Agents Chemother. 2016; 60 (11): 6532-9.
12. Muniyappa R, Gubbi S. COVID-19 pandemic, Coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020; 318 (5): E736-E41.

13. Bocock JP. The proteoglycan testican-1 and PA-RING protein RNF13 as regulators of the lysosomal protease cathepsin L.Eur J Biochem. 2003; 270 (19): 4008-15.
14. Tzamaloukas AH, Avasthi PS. Acid-base disorders in hyperglycemia of insulin-dependent diabetic patients on chronic dialysis. J Diabetes Complicat. 1988; 2 (2): 75-8.
15. Maianski N, Geissler J, Srinivasula S, Alnemri E, Roos D, Kuijpers T. Functional characterization of mitochondria in neutrophils: a role restricted to apoptosis. Cell Death Differ. 2004; 11 (2): 143-53.
16. Hostetter MK. Handicaps to host defense: effects of hyperglycemia on C3 and Candida albicans. Diabetes. 1990; 39 (3): 271-5.
17. Zargar AH, Bashir MI, Masoodi SR, Laway BA, Wani AI, Khan AR, et al. Copper, zinc and magnesium levels in type-1 diabetes mellitus. Saudi Med J. 2002; 23 (5): 539-42.
18. Fogarty S, Hardie D. Development of protein kinase activators: AMPK as a target in metabolic disorders and cancer. Biochim Biophys Acta. 2010; 1804 (3): 581-91.
19. Takemura R, Werb Z. Secretory products of macrophages and their physiological functions. Am J Physiol Cell Physiol. 1984; 246 (1): C1-C9.
20. Fairweather D, Frisancho-Kiss S, Yusung SA, Barrett MA, Davis SE, Gatewood SJ, et al. Interferon-γ protects against chronic viral myocarditis by reducing mast cell degranulation, fibrosis, and the profibrotic cytokines transforming growth factor-β1, interleukin-1β, and interleukin-4 in the heart. The Am J Pathol. 2004; 165 (6): 1883-94.
21. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020; 38 (1): 1-9.
22. Zhao Q, Shepherd EG, Manson ME, Nelin LD, Sorokin A, Liu Y. The role of mitogen-activated protein kinase phosphatase-1 in the response of alveolar macrophages to lipopolysaccharide attenuation of proinflammatory cytokine biosynthesis via feedback control of p38. J Biol Chem. 2005; 280 (9): 8101-8.
23. Aronson D. Hyperglycemia and the pathobiology of diabetic complications. Cardiovascular Diabetology: Clinical, Metabolic and Inflammatory Facets: Karger Publishers; 2008. p. 1-16.
24. Hoeller D, Hecker CM, Dikic I. Ubiquitin and ubiquitin-like proteins in cancer pathogenesis. NatRev Can. 2006; 6 (10): 776-88.

Author's Contribution

RI, AZ, AZ, AJ, MZ, NA: Conception of study, acquisition of data, drafting of manuscript and approval of the final version to be published.