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IMPLICATIONS FOR THE MANAGEMENT OF GLUCOSE LEVEL IN COVID-19 PATIENTS TO REDUCE MORTALITY RATE: A REVIEW

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ABSTRACT

COVID-19 is a severe contagious disease caused by the SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2). From December 2019 to till now, this virus infection has spread very rapidly across more than 160 countries in the world. Severity of acute respiratory syndrome coronavirus increases significantly in patient suffering from diabetes. High proportion of patients suffering from the diabetes makes it the major risk factor and an important comorbidity for the COVID-19. Depending upon the global epidemiology, 20-50% of patients reported with the COVID-19 are also diagnosed with the diabetes. Considering the importance of linkage between severity of COVID-19 and diabetes, we aim to provide overview on the pathogenic linkage between diabetes and corona virus infection, current therapeutic approaches available to manage the blood glucose level to reduce the risk of death in COVID-19 patients.

KEYWORDS: Comorbidity, contagious.

INTRODUCTION

COVID-19 is an infectious disease caused by corona virus, a positive sense RNA viruses belonging to the coronoviridae family.[1] Severe respiratory Syndrome (SARS-COV) and Middle respiratory syndrome (MARS-COV) are the major previous outbreaks of coronavirus before December 2019. China is considered as zoonotic region of coronavirus disease (2019) infection as first case of active infection was reported in Wuhan city of China in 17 November as according to media reports of China.[2] China responded very quickly by sharing the information with the World Health Organization (WHO) about the outbreak and by informing international community about the causative agent. The WHO responded

quickly by issuing guidelines about the patients screening, diagnostic development, specimen collection and providing updated information about the outbreak.[3] WHO announced the official name of Coronavirus disease 2019 as COVID-19 a disease that effect the respiratory track of patients results in medical problems like pneumonia, fever, breathing difficulties and lung infections.[4] From January 2020 to till now, severe acute respiratory syndrome induced by coronavirus (SARS-CoV-2) has become the major epidemics disease.[5]

Epidemiological report of COVID-19 outbreak 2020 suggested that most of patients suffering from this disease also have other comorbidities such as hypertension, diabetes and cardiovascular diseases.[6] Further, patients diagnosed with the diabetes mellitus are at the major risk of getting infection and death from COVID-19 especially those aged 65 years or older. Although, the complete pathophysiological mechanism are yet to be fully understood. The better understanding of potential pathophysiological mechanisms at both basic and clinical of COVID-19 in patients with diabetes is the need of hour.[7]

General Characteristics of COVID-19

Symptoms and clinical features

Incubation period of coronavirus infection ranges from 2-14 days with a median period of approximately 5.6 days.[8] Most common symptoms of COVID-19 illness are fever, cough, breathing difficulties, sputum production, sore throat, headache, diarrhoea and dyspnoea.[9] Death occur by COVID-19 infection depends upon the immune status and age of patient. Patients having week immune system, age more than 70 and suffering from other comorbidities such as hypertension, diabetes are more prone to death induced by COVID-19 infection.[10] CT scan of patients suffering from COVID-19 revealed that abnormal changes such as acute respiratory syndrome, acute cardiac injury, peripheral ground glass opacities in both the lungs leads to the death of patient.[11]

Modes of transmission

Chinese health authorities suggested that there are main routes of transmission from the COVID-19: (1) droplet transmission (2) contact transmission (3) aerosol transmission[12] Droplet transmission occurs when an infected person cough or sneezes and respiratory droplets produced by him are ingested or inhaled by person is in close contact with infected person. Contact transmission occur when a person touches the object contaminated with the virus, and aerosol transmission occur when respiratory droplets of infected person mix with air and forming aerosols.[13]

Virus Replication and life cycle

Coronavirus life cycle can be divided into four stages: (1) Attachment and entry (2) Replicase protein expression (3) Replication and transcription (4) Assembly and release.[14,15] Initially, receptor binding domains (RBD) present on the S protein of the virion attached with the receptor in the host cell body. The primary determinant factor of the virus to infect the host body is the strength of S- protein-receptor interaction.[16,17] However, some species of corona virus utilizes the peptidase enzyme as the binding domain. After the attachment of virus with the host cell receptor, virus get enter into the cytosol.[18] Entry of the virus is accomplished by cathepsin induced S protein proteolytic cleavage. Following binding and entry, the next stage in lifecycle of coronavirus is the translation of replicase gene present in the virus RNA.[19] A slippery sequence (5′-UUUAAAC-3′) is used by the virus to express its two polyproteins which ultimately encodes its two replicase genes; large ORFs, rep1a and rep1b. After the expression of replicase complexes, synthesis of both genomic and sub-genomic RNA occurs. For the structural and accessory genes, sub-genomic RNA acts as mRNA. Synthesis of both the genomic and sub-genomic RNA occurs through the negative-strand intermediates.[20] Various cis-acting sequences are majorly required for the viral RNAs replication. Further, the fusion of leader and body TRS is the major important factor required for the virus replication.[21] After the RNA synthesis and replication, translation and insertion of S, E and M into the endoplasmic reticulum occur. Further, these proteins move into the golgi endoplasmic reticulum intermediate compartment through the secretory pathway. After the assembly of the virion proteins, transportation of the virion across the vesicle occur and its release its proteins by exocytosis.[22]

Pathogenesis and diagnosis

Significant rise in the leukocyte number, rise in the level of pro-inflammatory cytokines and abnormal findings in the lower respiratory tract of patients are some of most prominent pathogenic features in the patients infected with COVID-19.[23]

Laboratory confirmed case of one of the COVID-19 presented patient with the abnormal breathing sound in both the lungs, leucopoenia with increase in the number of leukocyte, high value of blood C-reactive protein as shown in figure.[24] Further, D-dimer and increased sedimentation rate of RBC was also observed. Significant rise in the blood level of pro-inflammatory cytokinins such as interleukins and tumour necrosis factor-alpha was observed

in patients admitted to the intensive care unit with COVID-19 infection that increase the severity of disease.[25]

RT-PCR (Real time polymerase chain reaction) has been suggested as diagnostic procedure to confirm the COVID-19 infection in suspected patients. Presence of positive nucleic acid of COVID-19 in sputum, swabs and secretions of lower respiratory tract is confirmed with the RT-PCR and further confirmation is done by next-generation sequencing.[26]

COVID-19 and other comorbidities

Most severe deadly cases with COVID-19 have reported in elder patients or in patients suffering from other underlying diseases such as severe lung, cardiovascular diseases, hypertension, diabetes, and cancer. However, complete pathophysiological mechanism behind it is not clear.[27]

Potential association between COVID-19 and diabetes

Diabetes, a metabolic disorder, characterized by elevated level of glucose in the blood. It is the major contributor of mortality and morbidity throughout the world.[28] It leads to various other serious micro and macro vascular complications which affect the patient life. A clinical association between diabetes and other infectious diseases has long been recognized. Infectious diseases such as influenza, pneumonia are most commonly occurring in the people diagnosed with diabetes.[29]

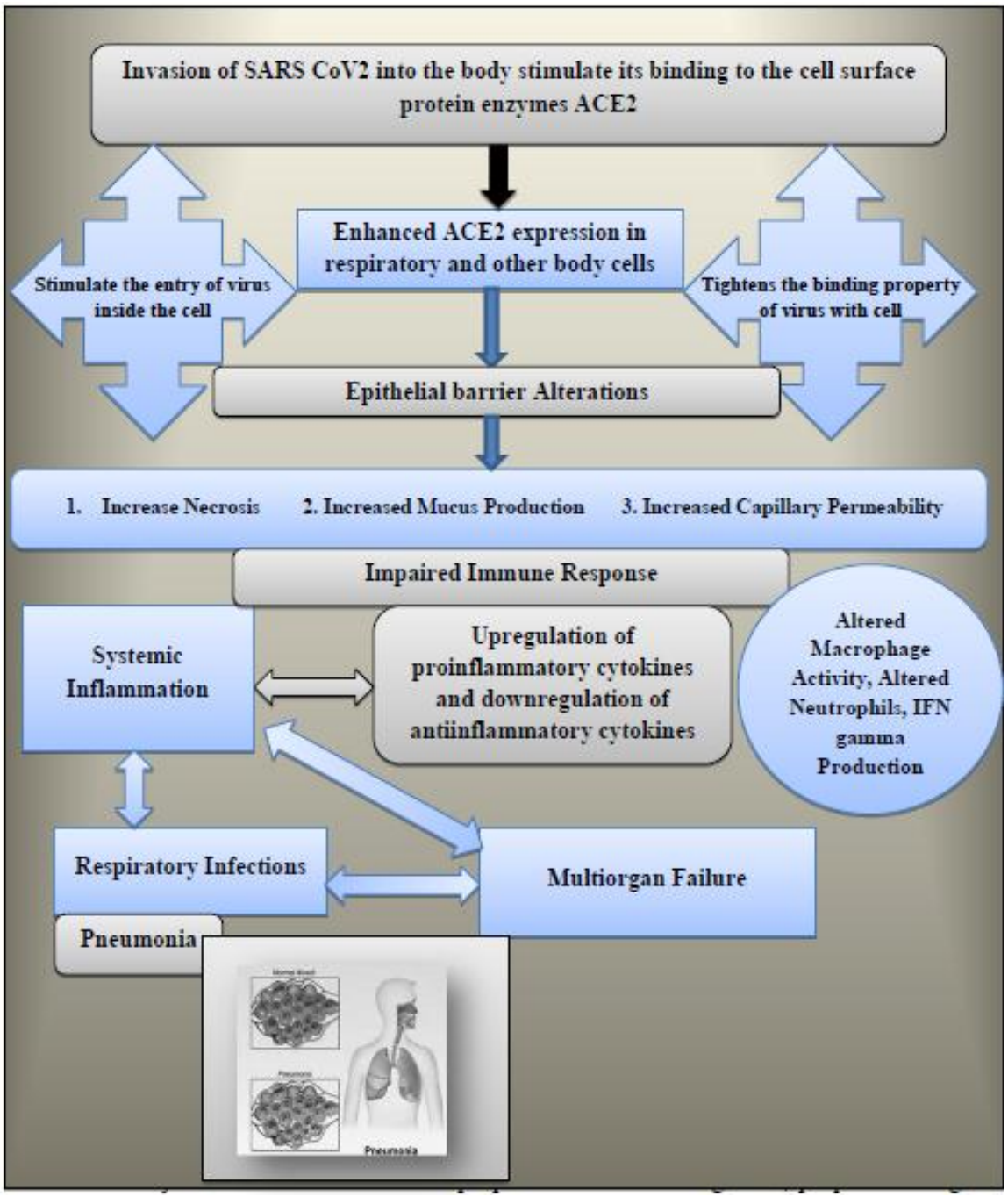

Figure: Diabetes Patients with enhanced susceptibility of corona virus.

Centre for Disease Control and Prevention (CDC) and other national health centres and hospitals from epidemiological study showed that Diabetes was a major contributing factor of high severity and mortality in Middle East Respiratory Syndrome (MERS-CoV).[30] Further, in this study it was also observed that risk of serious complications and death frequency is 50% higher in patients from COVID-19 with diabetes than the patients having controlled level of glucose.[31] Various hypotheses are demonstrated to validate the increased frequency and severity of COVID-19 infection in people with diabetes. In general, people suffering

from type 1 and type 2 diabetes are highly susceptible to suffer from other infectious diseases because of severe changes occur in events involved in cell mediated and innate immunity system.[32] Various abnormal physiological and biochemical changes occur in diabetes make the patient susceptible to COVID-19: (1) significant increase in affinity of virus to bind with the host body cell (2) decline in the clearance of virus from the body (3) reduction in the functioning of immune cells (4) modulation in the inflammatory response of body to pathogenic microorganisms.[33]

Diabetes is severe inflammatory condition characterized by high level of glucose in blood and insulin resistance. Several metabolic and vascular abnormalities in diabetes affect the response of human body to pathogenic microorganisms.[34] Further, hyperglyceamia and insulin tolerance occur in diabetes modulate the production of reactive oxygen species, pro-inflammatory cytokines, glycosylation end products (AGEs) that potentiate the inflammation in tissue.[35] This inflammatory process may compose the underlying mechanism that leads to a higher propensity to infections, with worse outcomes thereof in patients with diabetes.[36]

Binding affinity of SARS-CoV-2 may increased due to modulation in the expression of ACE2 in myocardium, kidney, alveolar AT2 cell and pancreas.[37-38] Roca-Ho H et.al by animal study demonstrated that expression of ACE2 receptors increased in DM. Administrations of drugs such as thiazolidinediones, pioglitazone, liraglutide used for the treatment of diabetes leads to up-regulation of ACE2. Further, Roca Ho H et.al by animal study demonstrated that expression of ACE2 receptors increased in DM demonstrates the hypothesis of increased expression of using the phenome-wide Mendelian randomization study. Results of this study indicate that expression of ACE2 increased significatly in lungs in patients with DM.[39] Further level of protease enzyme (furin), get increased in DM patients. This enzyme potentiates the virus entry in host body by facilitating the cleavage of the SI and S2 domain of the spike protein.[39] Chen X et.al analysed clinical and laboratory data of 106 COVID-19 hospitalized patients who in the Zhongnan Hospital of Wuhan University, Wuhan, China. Results of this study provide evidence that virus clearance from host body get delayed in patients suffering from diabetes.[40]

Implications for diabetic management

People suffering from diabetes should give special attention on their metabolic control as primary prophylactic method of COVID-19 disease.[41] This involves the strict follow up of the diet restrictions recommended by the consultant to control blood pressure and lipid levels.

All patients with COVID-19 disease and diabetes require regular control of glucose level to reduce the risk of death.[42] Health care consultant should also encourage the patients with to follow precautionary measures such as hand washing and physical distancing recommended by the WHO, the CDC, and state and local governments.[43]

Treatment of hyperglycaemia and other associated metabolic conditions

Most of the patients suffering from type 2 diabetes have also various other metabolic diseases such as hypertension and dyslipidaemia.[44] Therefore, prescribing the treatment of various antihypertensive and lipid reducing medications is of utmost importance to manage the metabolic syndromes.

ACE2 and angiotensin 2 receptor blockers drugs used in the management of hypertension could potentiate the virus entry into body cells by modulating the expression of ACE2. However, a statement given by the European Society of Cardiology and the Heart Failure Society of America, American College of Cardiology, American Heart Association provide evidence that ACE2 and angiotensin 2 receptor blocker could protect the host body from severe lung damage induced by the SARS-CoV. Therefore, these drugs should be continuously used for the management of hypertension.[45]

High level of lipids in the body (hyperlipidaemia) occur in diabetes reduces the expression of ACE2 receptors. Statins, most commonly drugs for the treatment of hyperlipidaemia, modulate the expression of ACE2 receptors by their anti-inflammatory effect.[46] However, as increase in the expression of ACE2 receptors can increase the susceptibility of patients towards COVID-19. Even then statins drugs should not be discontinued because of their long term potential therapeutic effects. These drugs protect the severe pneumonia with bacteraemia or sepsis by antagonizes the secretion of iIL-8, neutrophils chemotactic factor.[47]

Special consideration might be given to the certain groups of people suffering from the diabetes. Level of haemoglobin are rise significantly in patients suffering from diabetes lead to dysfunctioning of defence system of body which make the patient more susceptible to suffer from other infectious disease.[48] Those patients with elevated haemoglobin level will need regular intense monitoring to decrease the risk of metabolic disorders including diabetic ketoacidosis.[49,50] Further, chronic diabetic ketoacidosis (DKA) cases has been observed more prominently in patients diagnosed positive with COVID-19 with established type 1 diabetes. Thus it become very important to manage DKA in type 1 diabetes patients by taking

various preventive measures such as making them aware about this complication, informed them about the typical symptoms, and acute behaviour guideline.[51]

Overweight or obesity is also present in most of the patients suffering from diabetes.[52] Body mass index is important key factor of hypoxia management by mechanical ventilation, respiratory volume. Therefore, risk of ventilation failure could increase in patients with high body mass index and diabetes. Clinical experience in treating young patients with obesity and COVID-19 justify this evidence.[53]

Special considerations on use of diabetes drugs

Inadequate control of glucose level increases the susceptibility towards the other infectious diseases. So, by optimizing the control in the level of glucose in body, risk of infectious diseases can be reduced.[54] But presence of several infectious diseases poses a major challenge in the treatment of diabetic patients. Frequent monitoring of blood glucose level and special consideration for changes in antidiabetic treatment should be made to eliminate the risk of severe COVID-19 disease.[55]

Metformin and SGLT-2 inhibitors antidiabetic drugs are used for the management of moderate to severe illness.[56] However, these drugs are associated with metabolic abnormalities such as lactic acidosis by metformin, ketoacidosis with SLGT-2 inhibitors. Therefore, these antidiabetic drugs should be discontinued for the treatment of COVID-19 severe illness.[57] Further, hypoglycaemia can be induced by sulfonylurea drugs used for treatment of diabetes. Treatment with the insulin will becomes the alternative choice of treatment and will be preferred for the patients where this option is feasible.[58] But, treatment with the insulin administration is complicated as of restriction in time for titration of insulin. Intravenous infusion method should be used to manage the high insulin dose administration in patients.[59] Important consideration is required to manage the fluid balance in patients receiving the insulin treatment as excess fluid consumption can induce the pulmonary oedema.[60] Further, decline in potassium balance is as common complication occurs in COVID-19 patients, so maintaining the potassium level following treatment with insulin should be carefully maintained.[61]

Insulin pump therapy or basal bolus insulin is used for the treatment of type 1 diabetic patients. However, insulin doses should be titrated prior before usage to reduce the frequency of hypoglycaemia and ketoacidosis.[62]

CONCLUSION

Diabetes is linked with the increased severity, incidence and mortality rate of COVID-19. Experimental clinical and animal studies provide strong evidence about the influence of diabetes on the entry of virus into the host cell and inflammatory response to the infection. So, it becomes very important to control the glucose level in patients diagnosed with COVID-19. Various innovations such as telemedicine can be helpful in these challenging periods where strict movements on restrictions are present. Executing clinical trials under challenging circumstances has been proven feasible during the COVID-19 pandemic, and trial networks to provide evidence-based therapies are arising. Investigating subgroups with diabetes and how these relate to COVID-19 outcomes will be important; in particular investigating if some of the various management approaches would be particularly effective in managing diabetes in a COVID-19 context. During the COVID-19 epidemics, execution of clinical trails to investigate the various treatment approaches would be significantly effective in managing group of people suffering from diabetes in COVID-19 context.

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