THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

THE PATHOPHYSIOLOGY OF COVID-19 DISEASE IN DIABETES MELLITUS

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Accepted October, 29, 2020

Endocrinological affections are aggravated by the COVID-19 disease. The SARS-CoV-2 virus hastens the symptoms severity in diabetic patients and it manifests for such patients through hyperosmolar hyperglycemic state, diabetic ketoacidosis and insulin resistance. The severity of the symptomology is associated with old age, obesity (body mass index > 40 kg/m^2) and other medical comorbidities. Type 2 diabetes mellitus comes with sever complications which requires hospitalization, intubation and intensive care and presents risk of death due to VOID-19 disease. Diabetes mellitus represents by itself an independent factor for the symptomatology of SARS-CoV-2 infected patients. The inflammatory trigger from COVID-19 disease together with the pro inflammatory status of diabetic patients and the expression of angiotensin-converting enzyme (ACE) receptors play a key role in the symptomatology severity of diabetes patients infected with SARS-CoV-2.

Keywords: T2DM, cytokine storm, IL-6, SARS-CoV-2.

INTRODUCTION

Diabetic patients show a much more severe symptomatology of the disease in the presence of the SARS-CoV-2 virus[1]. The relation between old age, associated comorbidities and obesity is tightly correlated with the severity of the diabetes and furthermore these are independent prediction factors for COVID-19 mortality rate[2,3]. Type 2 diabetes mellitus was more frequently associated with sever manifestations of the COVID-19 disease, many of the COVID-19 patients being also found with diabetes[4,5]. Special considerations are required regarding the complexity of therapeutically management of diabetes patients with COVID-19 disease as well as for the negative impact of SARS-CoV-2 infection on diabetes[6].

The SARS-CoV-2 virus latches to the angiotensin conversion enzyme 2 (ACE2) through the spike protein and under the action of a transmembrane protease serine TMPRSS22 the viral infectivity is triggered[5]. Virus replication is done in the type II and type II pneumocytes and leads to severe acute respiratory syndrome.

The hyper inflammatory status from diabetes mellitus together with the cytokine storm from COVID-19 aggravates the two diseases which results into a rapid deterioration of the patient's health leading towards death. Cytokine release syndrome shows preexistent fever with acute phase reactants elevated (C-reactive protein, D-dimer, ferritin) as well as raised pro inflammatory cytokines (IL-6)[7].

Insulin resistance and hyperglycemia associates with a pro thrombotic state in which there are increased levels of fibrinogen, plasminogen activator inhibitor-1 (PAI-1) and increased platelet aggregability. Increased activity of protein kinase C (PKC) leads to the increase of endothelin-1 (ET-1) which increases the vasoconstriction and platelet aggregation in diabetes mellitus[8–10].

Hypercoagulability in COVID-19 disease can be included in Virchow's triad: endothelial injury, stasis and hypercoagulable state that leads to microvascular thrombosis and risk of venous thromboembolism and for very ill patients the criteria for disseminated intravascular coagulation (DIC) are met[7,11].

CYTOKINE STORM IN COVID-19 DISEASE

Cytokine release syndrome (CRS) or cytokine storm appears as result of the immune system hyper activation. CRS trigger is given by the gamma interferon (IFN-γ) released from T activated cells. IFN-γ activates macrophages, which in turn triggers the secretion of interleukin-6 (IL6), interleukin-10 (IL-10) and tumor necrosis factor alpha (TNF-α). Other cytokines raised in CRS are IL-1, IL-5, IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Increase of IL-6 is associated with vascular alterations; activation of the coagulation cascades and activation of complement and in severe cases lead to disseminated intravascular coagulation. IL-6 is one of the most important cytokines involved in the pathophysiology of COVID-19 disease. In this regard, in order to interrupt the IL-6 signaling pathway, therapy with tocilizumab – IL-6 receptor antagonist was attempted[12].

Raised IFN-γ is associated with fever, headache, chills, fatigue and dizziness. Malaise, diarrhea and fever are symptoms of flu; vascular abnormalities, overproduction of acute phase proteins and lung injury are associated with elevated TNF-α.

T cell activation amplifies the release of cytokines and acute phase reactants; endothelial cells lead to coagulopathy and capillary leakage.

Clinical manifestations of CRS are flu like with variability between individuals which can go even up to systemic inflammatory response syndrome (SRIS). Mild symptoms such as headache, diarrhea, arthralgia, fatigue, myalgia and rash accompanied by fever show an accelerated deterioration in the presence of T2DM and can lead to hypotension, circulatory/vascular collapse, cardiac dysfunction, pulmonary edema, renal insufficiency and multiorgan system failure. In diabetes mellitus the SARS-CoV-2 infection precipitates hyperosmolar hyperglycemia, diabetic ketoacidosis and insulin resistance[13].

ISSUES ASSOCIATED IN DIABETES PATIENTS WITH COIVD-19 DISEASE

For hyperglycemic diabetes patients admitted with moderated or sever COVID-19 disease the hyperglycemia treatment with insulin is preferred. The glycemic target is between 40–170 mg/dl (7.8 to 10 mmol/L).

Moderate diabetic ketoacidosis, defined through ph □ 7, serum bicarbonate > 10 mEQ/L, serum potassium > 3.3EQ/L, plasma glucose > 250 mg/dl (> 13.9 nmol/L) and mental status affliction is precipitated by the COVID-19 disease at diabetic patients. The hyperosmolar hyperglycemic state is precipitated by the SARS-CoV-2 infection with plasma glucose > 600 mg/dL (>33.3 nmol/L), serum bicarbonate > 18 mEq/L and arterial ph > 7.30.

Sever insulin resistance precipitated by the SARS-CoV-2 infection in diabetes patients was improved with the COVID-19 disease resolution, which raises the suspicion of correlation with the cytokine storm, in particular the IL-6 mediated[1,14].

CLINICAL PRESENTATIONS

T2DM associates sever complications, intensive care units and death from COVID-19 disease compared with T1DM. Pneumonia is with fever, cough, dyspnea, diarrhea, loss of smell or taste, myalgia, headache, sore throat, nausea and vomiting. Respiratory failure is the most feared manifestation of the disease and requires mechanical ventilation. Thromboembolic complications appear due to the hypercoagulability status[5,13,15].

The association of hyper inflammatory status from diabetes, especially the expression of IL-6 and metabolic syndrome with obesity represents a significantly greater risk for the cytokine storm from CVOID-19 compared with non-diabetes patients. Increased D-dimer and association with hypercoagulability status in diabetic patients have a negative impact in SARS-CoV-2 infection. Hyperglycemia in virus infected patients and with diabetes mellitus aggravates the symptomatology with metabolic decompensation, which raises the risk of admittance in intensive therapy units and appearance of cardiovascular, respiratory and renal complications which have an unfavorable prognosis. Glycemic imbalances followed by acute complications can rise in patients previously controlled glycemic wise but infected with SARS-CoV-2[13,16].

CONCLUSIONS

Rigorous control of diabetes mellitus significantly limits the risk of infection and precipitation of events with unfavorable prognosis. Diabetes mellitus is a major risk for COVID-19. The insulin treatment is preferred to the oral antidiabetics since these associate complications which aggravates the state of the diabetic patient infected with SARS-CoV-2. The risk factors for diabetic patients with COVID-19 are hypertension, cardiovascular disease, renal disease, pulmonary disease and cancers[7,17].

Prevention in diabetic patients through limitation of intercommunity transmission and reduced exposure through social distancing along the general protection measures, reduces the acute complication and death risk which can come due to SARS-CoV-2 infection[18,19].

Infection control is achieved through hand hygiene, respiratory hygiene (covering of nose and mouth when sneezing or coughing), avoiding face touching, especially of the eyes, nose and mouth, telephone disinfection and of the surfaces with contamination potential which are frequently touched, ventilation of close spaces and wearing of masks. All these measures help prevent the spreading of the virus[20].

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