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Relationship between Diabetesand Susceptibility to COVID-19

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ABSTRACT:
Coronavirus disease 2019 (COVID-19), triggered by the severe acute respiratorysyndrome-coronavirus 2 (SARS-CoV-2), may lead to extrapulmonary manifestationslike diabetes mellitus (DM) and hyperglycemia, both predicting a poor prognosisand an increased risk of death. SARS-CoV-2 infects the pancreas throughangiotensin-converting enzyme 2 (ACE2), where it is highly expressed compared to otherorgans, leading to pancreatic damage with subsequent impairment of insulin secretionand development of hyperglycemia even in non-DM patients.SARS-CoV-2 infection impairsglucose homeostasis and metabolism in DM and non-DM patients due to cytokinestorm (CS) development, downregulation of ACE2, and direct injury of pancreaticb-cells. Therefore, the potent anti-inflammatory effect of diabetic pharmacotherapiessuch as metformin, pioglitazone, sodium-glucose co-transporter-2 inhibitors (SGLT2Is),and dipeptidyl peptidase-4 (DPP4) inhibitors may mitigate COVID-19 severity. In addition,some antidiabetic agents and also insulin may reduce SARS-CoV-2 infectivity andseverity through the modulation of the ACE2 receptor expression. The findings presentedhere illustrate that insulin therapy might seem as more appropriate than other anti-DMpharmacotherapies in the management of COVID-19 patients with DM due to low riskof uncontrolled hyperglycemia and diabetic ketoacidosis (DKA). From these findings,we could not give the final conclusion about the efficacy of diabetic pharmacotherapy inCOVID-19; thus, clinical trial and prospective studies are warranted to confirm this findingand concern.

Keywords: Diabetes mellitus, SARS-CoV-2,Hyperglycemia

I. INTRODUCTION:

Coronaviruses are enveloped, positive single-stranded RNA viruses widely distributed in humans and animals worldwide (Huang et al.,2020, Isam et al., 2021). Although most human coronavirus infections are mild, major outbreaks of two betacoronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, have caused deadly pneumonia, with mortality rates of 10% for SARS-CoV and 36% for MERS-CoV. In December 2019, clusters of pneumonia cases of unknown etiology emerged in Wuhan, Hubei Province, China. Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus as the causative agent, which was named Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), and the disease it causes called COVID-19 (WHO,2020). Although SARS-CoV-2 has shown phylogenetic and clinical similarities with SARS-CoV, the novel coronavirus appears to have a higher transmissibility and lower case fatality rates . On 30 January 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern, and on March 11, the epidemic was upgraded to pandemic (WHO,2020). As of today (02.04.2020), 827,419 confirmed cases are officially reported in more than 200 countries or territories with 40,777 deaths . We conducted a scoping review to provide a brief summary of the general characteristics of COVID-19, as well as a more detailed description and critical assessment of the association between this new infectious disease and diabetes. We hope this review can provide meaningful information for future research and ultimately contribute to better clinical management of patients with COVID-19 and diabetes.

This new CoV infection called as COVID-19 originated in Wuhan, Hubei Province, China in December 2019 (Zhu et al.,2020). The causative agent for this respiratory illness is severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) . These epidemics have a high infection transmission rate and in general, the direct cause of death is severe atypical pneumonia (Yin and Wunderink ,2018) .The disease spread rapidly from

the initial epicenter, Wuhan to rest of the world and has become a pandemic. The main risk factors include pneumonia, acute kidney failure, acute heart failure. People with underlying health conditions such as cardiovascular disease, diabetes, chronic respiratory disease and the elderly above 60 years are most susceptible to COVID-19. Hospitals announced a cluster of cases of unknown cause pneumonia in Wuhan, Hubei, China on 31 December 2019, attracting great national and worldwide attention.Coronavirus (CoV) is a wide family of single-stranded , positive-sense RNA viruses belonging to the Nidovirales order.The order includes families of the Roniviridae, Arteriviridae, and Coronaviridae. The family Coronaviridae is subdivided into subfamilies Torovirinae and Coronavirinae. Coronavirinae is further subclassified into alpha, beta, gamma and delta COVs(Fehr and Perlman.,2015)Phylogenetic clustering accounts for certain virus subtypes being named. The viral RNA genome varies in length from 26 to 32 kilobases. They can be separated from various species of animals. Those include birds, cattle and mammals such as camels, bats and masks Civets of leaves, rats, pigs, cats . The widespread COV distribution and infectivity make it a major pathogen. The moderate clinical signs are associated with human pathogenic subtypes of CoV. Yet extreme coronavirus-related acute respiratory syndrome (SARS-CoV) and the Middle East The two notable exceptions are respiratory coronavirus syndrome (MERS-CoV). In Saudi Arabia MERS-CoV was first observed in 2012. It has been responsible for 2,494 confirmed cases which have resulted in 858 deaths. In 2002, a Beta-COV subtype spread rapidly in Guangdong , China. In 37 countries this epidemic resulted in 8,000 infections and 774 deaths(Lauet al.,2020)The COVID-19 pandemic spurred a crisis that is unprece-dented in modern times (Zhuet al.,2019). The disease course variessubstantially among individuals, from mild or even sub-clinical infection to severe disease .Indeed, more than1 million COVID-19-related deaths have been reportedglobally. There is interest in potential risk factors thataffect susceptibility to infection and disease progression.Multiple medical (e.g. diabetes, hypertension) andsociodemographic (e.g. sex, age and race/ethnicity) riskfactors for severe outcomes were already established (Wiersingaet al.,2019).

Association between COVID-19 anddiabetes

Diabetes is one of the leading causes of morbidity and mortalitythroughout the world. The condition is associated withseveral macrovascular and microvascular complications, thatultimately impact the overall patient's survival (Williamset al.,2020) . A relationshipbetween diabetes and infection has long been clinicallyrecognized . Infections, particularly influenza andpneumonia, are often common and more serious in olderpeople with type 2 diabetes mellitus (T2DM) . Neverthelessthe evidence remains controversial regarding whetherdiabetes itself indeed increases susceptibility and impactsoutcomes from infections, or the cardiovascular and renalcomorbidities that are frequently associated with diabetesare the main factors involved .Diabetes and uncontrolled glycaemia were reported as significantpredictors of severity and deaths in patients infectedwith different viruses, including the 2009 pandemic influenzaA (H1N1) , SARS-CoVand MERS-CoV (BanikGouri Raniet al.,2016) . In the currentSARS-CoV-2 pandemic, some studies did not find a clearassociation between diabetes and severe disease . However,other reports from China and Italy showedthat older patients with chronic diseases, including diabetes,were at higher risk for severe COVID-19 and mortality.Scarce data exist regarding glucose metabolism and developmentof acute complications of diabetes (e.g., ketoacidosis)in patients with COVID-19. Infection of SARS-CoV-2 in thosewith diabetes possibly triggers higher stress conditions, withgreater release of hyperglycemic hormones, e.g., glucocorticoidsand catecholamines, leading to increased blood glucoselevels and abnormal glucose variability (Wang Aihonget al.,2020). On the otherhand, a retrospective study fromWuhan reported that around10% of the patients with T2DM and COVID-19 suffered at leastone episode of hypoglycemia (<3.9 mmol/L). Hypoglycemiahas been shown to mobilize pro-inflammatorymonocytes and increase platelet reactivity, contributing to ahigher cardiovascular mortality in patients with diabetes(Iqbalet al.,2019). Yet it remains largely unknown how exactly the inflammatoryand immune response occurs in these patients, aswell as whether hyper- or hypoglycemia may alter theSARS-CoV-2 virulence, or the virus itself interferes with insulinsecretion or glycemic control. Furthermore, the impact ofusual diabetes drug treatment on COVID-19 outcomes, as wellas therapeutic approaches for COVID-19 on glucose regulationremains unspecified.Diabetes is a chronic inflammatory condition characterizedby multiple metabolic and vascular abnormalities thatcan affect our response to pathogens. Hyperglycemiaand insulin resistance promote increased synthesis of glycosylationend products (AGEs) and pro-inflammatory cytokines,oxidative stress, in addition

to stimulating theproduction of adhesion molecules that mediate tissue inflammation. This inflammatory process may compose theunderlying mechanism that leads to a higher propensity toinfections, with worse outcomes thereof in patients with diabetes(Knapp Sylvia ,2013).Several defects in immunity have been associated withhyperglycemia, even though the clinical relevance of somein vitro disturbances are still not fully understood . Poorlycontrolled diabetes has been linked to inhibited lymphocyteproliferative response to different kinds of stimuli , as wellas impaired monocyte/macrophage and neutrophil functions(Knapp Sylvia,2013). Abnormal delayed type hypersensitivity reaction andcomplement activation dysfunction have also beendescribed in patients with diabetes. In vitro studies haveshown that pulmonary epithelial cells exposure to high glucoseconcentrations significantly increases influenza virusinfection and replication, indicating that hyperglycemia mayenhance viral replication in vivo . In animal models, struc-tural lung changes have been related to diabetes, such as augmentedvasculature permeability and collapsed alveolarepithelium . On the other hand, patients with diabetesgenerally present a significant reduction in forced vital capacity(FVC) and forced expiratory volume in one second (FEV1),which is associated with raised plasma glucose levels (Popov and Simionescu .,1997).

Covid-19 and Hyperglycemia

It has been stated that COVID-19 is associated withhyperglycemia, actually considered a direct predictor of thepoor prognosis of the disease and to an increased risk of death. Briefly, the binding site and entry point of SARS-CoV-2is the ACE2 receptor, which is highly expressed in the lung,liver, brain, placenta, and pancreas. SARS-CoV-2 infects thepancreas through ACE2, being highly expressed there whencompared to other organs, leading to pancreatic damage withsubsequent impairment of insulin secretion and developmentof hyperglycemia even in non-DM patients. Similarly, SARSCoV-2-induced pancreatic injury may worsen a preexistentDM (Wanget al.,2020). Previous data have shown that SARS-CoV, which isclosely related to SARS-CoV-2, triggers transient hyperglycemiaand impairment of pancreatic b-cell function during epidemicderivedpneumonia. Moreover, the COVID-19-inducedinflammation and cytokine storm (CS), which are characterizedby profound elevations in the levels of tumor necrosis factoralpha(TNF-a) and interleukin (IL)-6, lead to peripheral insulinresistance (IR) . Besides, high TNF-a and IL-6 in CSimpair pancreatic b-cell function and inhibit insulin secretion.Taken together, both IR and impairment of pancreatic b-cellfunction contribute to a vicious cycle in the development andprogression of hyperglycemia in COVID-19 patients .Furthermore, hyperglycemia and induced oxidative stress andgluco-lipotoxicity contribute to the development of IR andimpairment of pancreatic b-cell function (Mehtaet al.,2020). In addition,prolonged hyperglycemia could worsen the course of COVID-19 via glycation of pancreatic ACE2, which facilitates theSARS-CoV-2 binding and entry at the pancreatic b-cell .Different reports have shown that an abnormal expression ofcell ACE2 receptors in different tissues reduces the protectiveeffect against viral entry and, consequently, exacerbates theseverity and poor outcomes of SARS-CoV-2 infection . Onthe other hand, the systemic renin-angiotensin system (RAS)regulates pancreatic b-cell function, while local RAS of pancreaticb-cell function controls b-cell apoptosis, cell proliferation, andoxidative stress (Al-kuraishyet al.,2021). Angiotensin II (AngII) through AT1Rleads to DM induction in experimental models, while inhibitingthe glucose-stimulated insulin secretion. Therefore, blockade ofAT1R improves pancreatic b-cell function and increases thepro-insulin and insulin biosynthesis. Besides, upregulated localpancreatic AngII induces oxidative stress that triggers b-celldamage by NADPH oxidase induction .Indeed, it has beenshown that hyperglycemia upregulates AT1R leading to b-cellfunction impairment and insulin secretion .In COVID-19, ACE2 dysregulation by SARS-CoV-2 leadsto marked elevation of vasoconstrictor AngII with a reductionin the vasodilator Ang1-7, which per se leads topancreatic b-cell dysfunction, inhibition of insulin secretion,and hyperglycemia, which might be transient even in non-DM patients. Furthermore, elevated AngII leads topulmonary vasoconstriction, ALI, and ARDS with the inductionof inflammation cascade and oxidative stress, which togetherparticipate in the induction of pancreatic b-cell function andhyperglycemia (Dwi and Netra,2020). Then, hyperglycemia in COVID-19 leadsto ALI through the induction of pulmonary sodium-potassiumchlorideco-transporter 1(NKCC1), involved in the regulation ofthe transport of water and ions to alveolar cells. Thus, untreatedand long-standing hyperglycemia may lead to ALI throughischemic-reperfusion injury . Also noteworthy is the factthat hyperglycemia is associated with oxidative stress' inductionand inflammatory mediators' overproduction, which togetherpartake in the development of endothelial

dysfunction andthrombosis due to alterations in both function and generation ofantithrombin III . Taken together, these findings reveal thatboth COVID-19 and hyperglycemia interact in a vicious cycleleading to more complications and worse metabolic outcomes (Al-Namiet al.,2019).

II. CONCLUSIONS

Suggestions are made on the possible pathophysiological mechanisms of therelationship between diabetes and COVID-19, and its management. No definite conclusionscan be made based on current limited evidence. Further research regarding this relationshipand its clinical management is warranted.Diabetes and other comorbidities are significantpredictors of morbidity and mortality in patients withCOVID-19. Future research is urgently needed to provide abetter understanding regarding potential differences ingenetic predispositions across populations, underlying pathophysiologicalmechanisms of the association between COVID-19 and diabetes, and its clinical management.

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