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Review Article

COVID-19 and Preexisted Diabetes, One Insults the Other "Narrative Review"

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Abstract

Diabetes mellitus is the commonest endocrine and metabolic disorders. Patients with diabetes have about double risk to develop severe COVID-19. The severity of COVID-19 shown to be associated with dysregulation of glycemic control in diabetes. This review focus on the most obvious contributing factors linking these nowadays the two common pandemics. A broad literature search been performed on Google Scholar and PubMed for the periods between 01/01/2021 and 01/03/2021. The search includes the followings key words; diabetes, COVID-19, SARS-CoV-2, corona virus, ACE2 and cytokines storm. Hyperglycemia and insulin resistance in diabetes patients acts as independent risk factors for acquiring severe covid-19 complication. ACE2 expression in diabetic patients is reduced but this reduction wasn't protective for gaining COVID-19 and even worsening the patient's outcomes. Exaggerated inflammatory responses in diabetics towards COVID-19 is obvious and serves to transform cytokines storm to a "Cytokine Super Cyclone". Both COVID-19 and diabetes mellitus affects each other and patients with diabetes subjected to have severe COVID-19 and with an increasing risk of mortality and worsening outcome. Diabetic persons should take great attention to keep their glycemic control as ideal as possible and it is essential to put them in the high priority list for gaining vaccination against COVID-19 virus.

Keywords: COVID-19, diabetes mellitus, ACE2, cytokines storm, inflammatory response, pandemic.

INTRODUCTION

Coronaviruses are single-stranded RNA viruses that broadly spread in humans and animals globally *(X. Yang et al*., 2020).Clinically, majority of infected individuals are mild, but minority of cases progress to severe acute respiratory distress syndrome leading to various organ failure and death.(Hussain, Bhowmik, & do Vale Moreira, 2020). Historically, two major outbreaks of Coronaviruses illness occur and lead to fatal pneumonia and high mortality rates. First; in 2002–2003 a severe acute respiratory syndrome coronavirus (SARS-CoV). Second outbreak reported as Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (Song *et al*., 2019). In approaching the end 2019, the latest outbreak of coronaviruses diseases has emerged in Wuhan, Hubei Province, China and spread globally caused by Severe Acute Respiratory Syndrome-Coronavirus-2.

(SARS-CoV-2), causing COVID-19 disease (Organization & Organization, 2020). The World Health Organization (WHO) in 30th of January 2020, announced that COVID-19 is an international Public Health Emergency and in March 2020 considered the outbreak to be a pandemic (Khan *et al*., 2021). Since then the world before COVID-19 is not as the same as after it, where millions of death reported world widely with catastrophic health care, economic and social drawbacks.

At early stage of COVID-19 infection, it is essential for the viruses to bind via their spikes to angiotensin converting enzyme type 2 receptors (ACE2) (Zou *et al*., 2020), and this represent the site of entrance of virus into the cells. The expression of the ACE2 essentially reported in the upper respiratory tract epithelial cells and in alveolar epithelial cells (type II) of the lung (H. P. Jia *et al*., 2005). Other tissues also shown to express ACE2 such as GIT cells, vascular endothelium, kidneys and even endocrine pancreas (Hikmet et al., 2020; Wang, Liang, & Leung, 2015). Thus, COVID-19 can cause multisystem illness.

It has been reported that the severity of COVID-19 disease is associated with comorbidities such as old age, hypertension, cardiovascular disease, cerebrovascular disease, diabetes, renal disease, chronic lung diseases and cancer (Hikmet *et al*., 2020; J. Yang *et al*., 2020; Zhou *et al*., 2020).

Preexistence diabetes and COVID-19

Diabetes is a chronic disease characterized by abnormally high blood glucose levels. Individuals with diabetes are underwent change in life's quality and subjected to substantial increasing risk of morbidity and premature mortality (Lovic *et al*., 2020). Pathophysiologically, diabetes mellitus results from either pancreatic β- cells destruction leading to insulin production insufficiency as in type 1 diabetes or resistance of insulin responsive tissues to the physiological level of insulin like that observed in type 2 diabetes resulting in hyperglycaemia (Nandhini, Kamalanathan, & Sahoo, 2019).

Currently, The estimated global prevalence is heralding and reaching up to 8.8% of the adult been considered diabetic and it is expected that by the year 2040 more than 690 million individuals will have diabetes if the risk factors not opposite (Ogurtsova *et al*., 2017). During COVID-19 pandemic, diabetes phenotype emerges as a high risk group for developing severe infection with worse progression of the disease. Comparing to non-diabetic subjects conducting COVID-19, diabetics' shown to have higher admission rates, more severe pneumonia and increasing mortality *(Kim et al*., 2020; S. Wang *et al*., 2020; Zhang *et al*., 2020). The exact pathophysiology of diabetic phenotype that is worsening the outcome of COVID-19 is not precisely confirmed. Several postulated mechanisms been adapted and could be categorized into five general abnormalities as shown in

Figure 1 and summarized in the followings;

1. Hyperglycemia and insulin resistance associated with severe COVID-19
2. Uncontrolled diabetes associated with compromised immune system.
3. Role of angiotensin-converting enzyme 2 (ACE2).
4. Diabetes represents a chronic pro-inflammatory state and hyper-coagulative states that could worsening COVID-19 outcome.
5. Treatment strategies of severe COVID-19 deteriorate metabolic state in diabetic subjects.

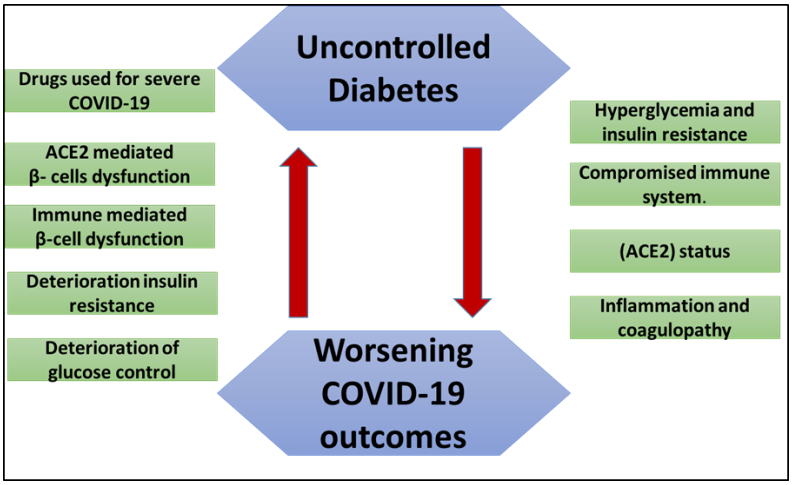

Fig-1: Representation diagram viewing the reciprocal interaction between the COVID-19 and diabetes mellitus. Uncontrolled Diabetes causes increase COVID-19 worsening outcomes through hyperglycemia and insulin resistance, compromised immunity, exacerbating inflammatory responses and low expression of (ACE2) in diabetic subjects or use of ACE inhibitors and ACE receptor blockers therapies. Contrary, severe COVID-19 affects glycaemia and worsening insulin resistance in diabetic patients via direct viruses mediated inflammatory responses, Immune mediated β-cell dysfunction, ACE2 mediated β- cells dysfunction and Drugs used in treatment of severe COVID-19 that shown to disturb glycaemia and glucose metabolism

Hyperglycemia represents a characteristic feature of diabetes both type 1 and 2. It was reported that hyperglycemia in diabetic patients admitted to hospital due to COVID-19 is associated with deteriorated patient prognosis (Corona *et al*., 2021; R. Gupta, Hussain, & Misra, 2020; Mantovani, Byrne, Zheng, & Targher, 2020). Furthermore, the severity of hyperglycemia been linked with worsening COVID-19 outcomes (Huang, Lim, & Pranata, 2020; Smith *et al*., 2021). A study conducted by Iacobellis, Penaherrera, Bermudez, and Mizrachi (2020) showed that acute hyperglycemia on admission represent major predictor of radiographic imaging of COVID-19 that could link hyperglycemia to exaggerated inflammatory response leading to progression of the radiographic findings. The mechanisms concerning the effects of hyperglycemia on worsening COVID-19 outcomes are variable. One postulated mechanism is that increase serum glucose level associated with pathogen virulence as well as reduce local interleukins production with impaired phagocytic activity (Casqueiro, Casqueiro, & Alves, 2012). Increase viral replication is also reported

in response to high glucose. A study performed on human monocytes showed that elevated glucose level is directly inducing COVID-19 replication(Codo *et al*., 2020).

A direct increase of glucose concentration within the airway secretion is also reported with hyperglycemia which could worsening local inflammation in response to viral infection (Philips, Meguer, Redman, & Baker, 2003). Moreover, hyperglycemia is direct cause of Non- enzymatic glycosylation of angiotensin-converting enzyme 2 (ACE2) that represent the receptor site of entrance of the virus into the pulmonary epithelial cells and this interaction come in favor of viral linkage to cellular receptors (Brufsky, 2020). In addition, overproduction of inflammatory mediator is a direct result of hyperglycemia that can lead to excessive tissues damage especially in cardiovascular system in response to COVID-19 infection (Antonio Ceriello *et al*., 2020)**.** Additionally, hyper coagulation and thrombosis, a dangerous scenarios of COVID-19 disease, are direct results of hyperglycemia which affect both increasing platelets activation and endothelial dysfunction (Antonio Ceriello, Zarich, & Testa, 2009) and reduce anti-thrombosis system (A Ceriello, 1993).

COVID-19 infection is also affect glycaemia in diabetic subjects. In diabetics, hyperglycemia and deterioration of glucose control are common complications of COVID-19 infection. In diabetics treated with insulin, it was observed that those patient became in increasing demands to get high insulin doses reaching up to 100 IU/day if they attached with COVID-19 and the dose showed to increase with the severity of infection (L. Wu, Girgis, & Cheung, 2020). Another surprising observation is that, COVID-19 patients with type 2 diabetes become subjected to have ketoacidosis, a common acute complication of Type 1 diabetes,. Pal, Banerjee, Yadav, and Bhattacharjee (2020) in their systematic review showed that in COVID-19 patient 77% of diabetics whom developed diabetic ketoacidosis were type 2 diabetic patients. These effects, hyperglycemia and diabetic ketoacidosis, are attributed to stress associated with critical situation that induce secretion of insulin antagonizing hormones such as glucocorticoid and catecholamines that facilitate increase blood sugar during COVID-19 infection.

Insulin resistance; defined as failure to response to the physiological level of insulin. Liver, adipose tissues and skeletal muscle represent insulin responsive tissues and best organs to reflect insulin resistance (A. Al-Bayati, Lukka, Brown, & Walker, 2016; Groop *et al*., 1989). Insulin resistance reported as another factor affecting severity and worse outcome of COVID-19 (Richardson *et al*., 2020). A study performed in Wuhan, china showed that the triglyceride and glucose index (TyG) in diabetic patients which is a predictor of insulin resistance shown to be directly associated with worsening outcome of COVID-19 patients (Ren *et al*., 2020). Obesity is another sign of insulin resistance shown to be a vital predictor of severity and need for intensive care of COVID-19 infarction. A large study conducted in France showed that the need of intensive care in COVID-19 patients was seven times more likely compared with normal body weight individuals (Simonnet et al., 2020). The fraudulent effects of obesity is both mechanical and metabolic (Stefan, Birkenfeld, Schulze, & Ludwig, 2020).

Hyperinsulinemia is additional marker of insulin resistance. Study showed that hyperinsulinemia is an independent factor responsible for pulmonary dysfunction in animal model (Leiria *et al*., 2015) that could add a risk of worsening outcome if getting COVID-19.

Non- alcoholic fatty liver disease (NAFLD) represents added sign of insulin resistance and metabolic syndrome. Both metabolic and inflammatory consequences associated with NAFLD shown to be strong predictors for bad prognosis of COVID-19 infection (Ji et al., 2020; Portincasa, Krawczyk, Smyk, Lammert, & Di Ciaula, 2020).

Inflammation and inflammatory cytokines represent the most important reported factor to induce insulin resistance. Several cytokines such as IL-6, TNF-α and adepokines shown to cause insulin resistance (A. A. H. Al-Bayati, 2017). These inflammatory markers also associate and potentiate multisystem complications observed with sever COVID-19 infection (Cheema *et al*., 2020).

COVID-19 infection represents a precipitating factor of deterioration insulin resistance in diabetic patients. Inflammatory response to severe COVID-19 infection can worsen insulin resistance. For example acute coronavirus pneumonia causes infiltration of inflammatory cells within the lung can affect liver and skeletal muscle insulin mediated glucose uptake (Lim, Bae, Kwon, & Nauck, 2020). Furthermore, severe COVID-19 infection can cause muscle weakness, lack of exercise and immobility to diabetes patients that further precipitates insulin resistance (Jose & Manuel, 2020), especially if we know that diabetic skeletal muscle cells shown to be less responsive to exercise (A. Al-Bayati, Brown, & Walker, 2019). Thus, both hyperglycemia and insulin resistance, corner stone signs of diabetes, regarded as independent factors that associated with worsening outcome of COVID-19, and patients with severe COVID-19 infection shown to have further worsening of insulin resistance.

Compromised immune system in uncontrolled diabetes is a risk factor for getting and worsening of different viral infection. Diabetes mellitus is not mere a syndrome of metabolic abnormalities but also

characterized by attenuated immunity state. Well recognized inflammatory changes are noted in both type 1 and type 2 diabetes. For example, a decrease in rate of infectious antigen attacking activity by neutrophils and macrophages due to impaired phagocytic rate. A suppressed chemokine responses are additional recorded changes in both diabetes type, as well as chronic high levels of pro-inflammatory mediators (Alexandraki *et al*., 2008; Marhoffer, Stein, Maeser, & Federlin, 1992).

The first line of defense mechanism, Innate Immune System, against different viral infections including COVID-19 shown to be attenuated in uncontrolled diabetes patients. Hyperglycemia due to uncontrolled diabetes is associated with impairment of different processes involving innate immune system such us; inhibition of phagocytosis, reduction of neutrophil migration, inhibition of production of cytoprotective superoxide that kills viruses, decrease initial inflammatory response represented by vascular dilation and increase permeability and reduce complement system activation via glycosylation of its proteins (Jafar, Edriss, & Nugent, 2016). Furthermore, diabetes regarded as low-grade inflammatory state characterized by chronic increase of interleukin-6, ferritin and C-reactive protein (Elimam, Abdulla, & Taha, 2019). These biomarkers has been described to be strongly associated with COVID-19 severity in patients with diabetes compared to non-diabetic patients (W. Guo *et al*., 2020). These observations in diabetes put the patients at a great risk for developing exaggerated inflammatory/immune response (cytokine storm) recorded in sever complication of COVID-19 such as acute respiratory distress syndrome, shock and multisystem failure. Moreover, adaptive immunity processes shown to reduce in diabetics. β-cell function impairment, diminish memory CD4+ T-cell response, IgG and IgM level reduction, immunoglobulins glycosylation and defective antibodies binding ability and Low levels of circulating complements components are collectively reported in uncontrolled diabetes (Pal & Banerjee, 2021). Defective adaptive immune response in diabetics not only associated with severe COVID-19 but also put the patients at great risk of clinical recurrences or re-positives (Gousseff *et al*., 2020; Zhu *et al*., 2020). Therefore, diabetes related defective immunity is associated with severe COVID-19 complication as well as increase the risk of reinfection.

Role of angiotensin-converting enzyme 2 (ACE2)

Angiotensin-converting enzyme 2 (ACE2) represents a convergence point for both diabetes and COVID-19. ACE2 are regarded as receptors for entry of the COVID-19 virus into the cells along with its role in cardiovascular system and diabetes. Two forms of ACE2 protein been identified; membrane-bound and free circulating fragments(Xiao, Sakagami, & Miwa, 2020). The membrane-bound ACE2 is a protein that shown to be widely expressed in variable tissues in addition to lung cells such as; gastrointestinal tract, kidney, endothelium, cardiac cells, bone marrow, spleen and pancreatic islets (Yang, Lin, Ji, & Guo, 2010), the broad expression of this protein could highlight the multisystem injury encountered with COVID-19. Physiologically, ACE2 plays an important role in Renin–angiotensin–aldosterone system. ACE2 has a counter-regulatory role to ACE that converts angiotensin I into angiotensin II (promotion of vasoconstriction, aldosterone secretion, raising oxidative stress and inflammation). ACE2 breaks down angiotensin I into smaller molecules angiotensin (1–9) and angiotensin (1–7) (Figure 2). The later fragment performs two important Physiological functions. In cardiovascular system, they act as a regulator of blood pressure through vasodilation and increase renal sodium and water excretion. The second vital function of this system is its modulation of local inti-inflammatory and anti-oxidant responses protecting against tissues injury including lung injury observed in different viral pneumonias (South *et al*., 2019). The expression and the activity of ACE2 in diabetes patients shown to be reduced probably due to glycosylation of protein or low grade inflammatory state and elevation of exudative stress accompanying diabetic state (Pal & Bhansali, 2020; Tikellis, Bernardi, & Burns, 2011). The imbalance in the ACE2 activation during severe COVID-19 infection in diabetes leading to increase level of angiotensin II and a decrease in angiotensin 1-7 and as a consequences raised in the proinflammatory response and sever lung injury or even multisystem failure (Bornstein, Dalan, Hopkins, Mingrone, & Boehm, 2020). This expression profile and enzyme imbalance in diabetic subjects could explain the devastating effects of COVID-19 severe lung injury and even ARDS in diabetes.

Furthermore, ACE2 shown to have role in glucose regulation. In an animal study, Ace2- knockout mice shown to have hyperglycemia due to beta cell dysfunction (Lu, Wang, Yuan, Li, & Li, 2014). Moreover, hyperglycaemia is noted in even in people without diabetes that could be attributed to effects of virus on ACE2 expression in pancreatic islet cells causing β- cells dysfunction (lesson from previous coronavirus SARS) (Yang *et al*., 2010).

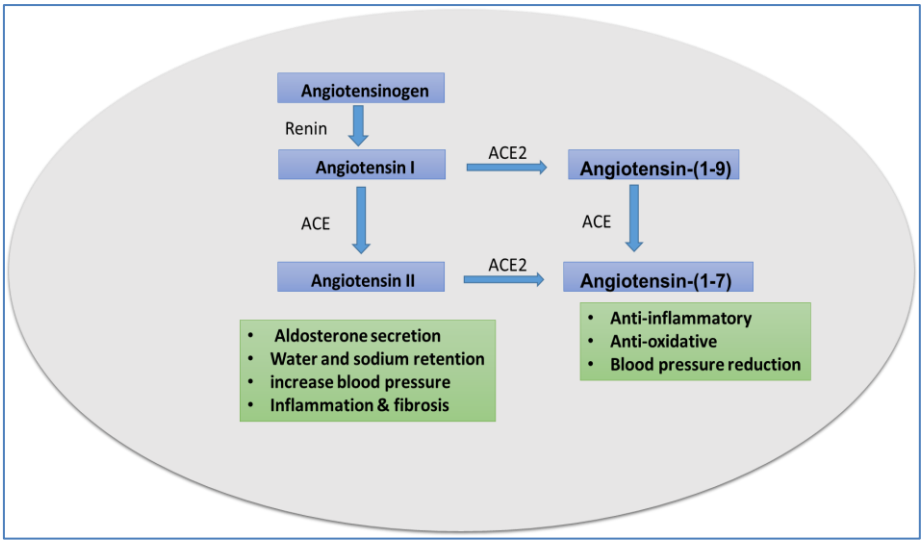

Fig-2: schematic representation for the physiological role of ACE2. ACE2 plays an important role in Renin–angiotensin–aldosterone system. ACE2 has a counter-regulatory role to ACE that converts angiotensin I into angiotensin II. Angiotensin II molecules facilitate promotion of vasoconstriction, aldosterone secretion, raising oxidative stress and inflammation. ACE2 breaks down angiotensin I into smaller molecules angiotensin (1–9) and angiotensin (1–7). The functions of angiotensin (1–7) molecules are regulation of blood pressure through vasodilation and increase renal sodium and water excretion. The second vital function is the modulation of local inti-inflammatory and anti-oxidant responses protecting against tissues injury.

Role of ACE inhibitors

Diabetes mellitus is usually associated with other comorbidities such as hypertension, cardiovascular diseases and diabetic nephropathy. Drugs commonly used for management of these illnesses are angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). Studies showed that the use of these pharmaceuticals leads to an increase of the level of expression of ACE2 peptide as a protective response to reverse the angiotensin II and angiotensin I resultant elevations (Cure & Cure, 2020a; Roshanravan, Ghaffari, & Hedayati, 2020). Two situations considered relating to the use of (ACEi) and (ARB). In one hand, the increase expression of ACE2 protein may enable easy entry and consequently proliferation of the virus and might lead to sever or even fatal COVID-19 infection (Fang, Karakiulakis, & Roth, 2020). However, it is shown to be apparent that once the viruses become inside the cells, ACE2 been degraded and loss its protective properties against lung injury (Pal & Bhansali, 2020). The decreased ACE2 expression in response to sever COVID-19 disease is furtherly supported by the reported a higher prevalence of hypokalemia due to increase urinary potassium loss that resulted from elevated angiotensin-II and aldosterone (Lim *et al*., 2020). Therefore, the use of (ACEi) and (ARB) that associated with ACE2 overexpression is not protective against severe lung injury due to COVID-19 and even worsening the outcome by facilitating viral entry.

On the other hand, the use of (ACEi) and (ARB) especially (ARB) has more than its known effects on decreasing blood pressure. The (ARB) usage shown to regulate multiple inflammatory and metabolic processes in patients on use such as, anti-inflammatory, reduction of fibrosis and endothelial injury, regulation of energy metabolism and insulin sensitivity, and additionally regulation of lipoprotein metabolism and normalization of coagulation processes (Gurwitz, 2020; H. Jia, 2016). Furthermore, less severe endothelial injury has been recognized in patients using (ARB) during viral pneumonia and septicemias (Fedson, 2016).

The controversy of the use of ACE relating drugs that observed during COVID-19 pandemic weather protective or harming effects is stand. A number of prestigious Societies (American Heart Association, European Society of Cardiology, the Heart Failure Society of America and the American College of Cardiology) recommended that doctors shouldn't discontinue these medications due to lack of vigorous data and proof (Cuschieri & Grech, 2020).

Inflammation and coagulopathy

The sever COVID-19 infection is characterized by overwhelming and defuse inflammatory landscapes. Eketunde, Mellacheruvu, and Oreoluwa (2020) summarized the main histopathological findings of post-mortems examination in patients whom died from severe COVID-19 as follow; in the lungs, diffuse alveolar injury and infiltration of inflammatory cell with noticeable thickening of hyaline membranes. Cardiac muscle inflammation is an additional observed critical finding. Likewise, hepatic tissues are infiltrated with lymphocytes with brain tissues have macrophage clustering and axonal damages. Other important findings are also reported such as focal pancreatitis and glomerular thrombosis. It is obvious that all these

findings reflect the disseminated inflammatory pathology.

Elevated serum inflammatory markers like ESR, CRP and ferritin are common findings for patients with severe COVID-19. Multiple inflammatory and immune mediators shown to be elevated in severe COVID-19 and correlated with disease severity and bad outcome of the disease. These inflammatory biomarkers include; IL-2, IL-6, IL-7, interferon-ɣ-inducible protein-10 (IP10), Tumor necrosis factor-α (TNF-α), Macrophage Inflammatory Protein (MIP-1α), monocyte chemoattractant protein-1 (MCP-1) and Granulocyte-colony stimulating factor (GCSF) (Blanco-Melo *et al*., 2020; Chen *et al*., 2020).

Furthermore, patients with severe COVID-19 undergo from vigorous formation of pro-inflammatory chemokines and cytokines but with an imbalance pro-inflammatory and pro-repair functions of cellular defense of lung (Acharya, Liu, & Gack, 2020). Thus, uncontrolled and exaggerated inflammatory responses may lead to the organ damage. The robust well-described inflammatory response to severe COVID-19 is "cytokine storm" in which IL-6 acts as a key biomarker and can lead to great risk of multi-organ failure and death *(Gao, Xu, Wang, & Liu, 2021; Leisman et al*., 2020). The elevated IL-6 shown to be inversely correlated with compromised immunity (especially T-cells) that demonstrated as lymphopenia in severe COVID-19 infection (Mazzoni *et al*., 2020). In the same aforementioned study (Mazzoni *et al*., 2020), showed that IL-6 is responsible for lymphopenia and attenuated cytotoxic defense mechanism against virus, and this observation confirmed by therapeutic use of IL-6 receptor antagonist (tocilizumab) that showed enhancement of in lymphocytes numbers and activities.

Diabetes mellitus is a syndrome of metabolic abnormalities characterized by chronic low-grade inflammatory state. Well recognized inflammatory changes are noted in both type 1 and type 2 diabetes. A raised pro-inflammatory markers is associated with impaired glucose metabolism, insulin resistance and insulin sensitivity, and are interconnected to type2 diabetes and microvascular complications resulted from diabetes (Navarro & Mora, 2005). Moreover, type1 diabetes pathogenesis is associated with high inflammatory mediators that infiltrate pancreas and causes β-cell destruction (Szablewski, 2014). Additionally, many genes related to cytokines production and activity have been identified as COVID-19- diabetes high risk group (Kumar, 2020). Diabetes patients with COVID-19 are associated with further increased of the inflammatory cytokines that can exacerbate severity and worsening outcome of the infection. Johnson and Laloraya (2020) in their valuable review stated a charming expression that Cytokine-storm of COVID-19 in diabetic patients can transformed to a Cytokine Super Cyclone.

For that, inflammation could be regarded as a "bridge" connecting diabetes with COVID-19, and the degree of inflammatory response determines the outcomes of the affected patients.

Coagulopathy is another emerging convergence point between diabetes and COVID-19 infection and progression. An Emerging evidence been observed that severe COVID-19 infection are associated with increased risk of thromboembolism (Al-Ani, Chehade, & Lazo-Langner, 2020). Three important factors related to the thromboembolism processes during COVID-19 been identified. These factors are systemic hyper inflammation, hypoxia and pre-existing comorbidities of the affected patients and diabetes on the top of the list of these comorbidities (Marchandot *et al*., 2020). Systemic inflammation acts as trigger for the tree arms of coagulation process namely platelets aggregation, endothelial dysfunction and coagulation cascade activation (Y. Wu, 2015).

Macrovascular thrombotic complications (venous and arterial thromboembolism) are reported with about One-third of hospitalized patients and associated with high risk in-hospital mortality (T. Guo *et al*., 2020). Furthermore, microvascular thrombosis is evident and recognized to be related to multi-organ failure associated with severe COVID-19 (Gando, 2010).

Hypoxia in COVID-19 patients represents a triggering factor for exacerbating coagulation process. Both inhibition of anti- coagulation and stimulation of coagulation processes are linked to the hypoxic environment (N. Gupta, Zhao, & Evans, 2019). Moreover, endothelial function towards anticoagulant properties are diminished and platelets hyper-activation are reported in response to hypoxia complicated COVID-19 (Cure & Cure, 2020b).

Diabetes represents a hypercoagulable state. Diabetic patients are subjecting to high risk of thrombotic and vascular events due to Hyper-coagulability (A. Al-Bayati *et al*., 2016). Hyperglycaemia in diabetic patients shown to increase risk of coagulation impair vascular endothelial dysfunction (Nieuwdorp *et al*., 2006). Thus, coagulopathy in COVID-19 shown to be boosted in diabetic subject and contributes to bad prognosis and unfavorable outcome of the disease.

Effects of drugs used for treatment of severe COVID-19 on diabetes

The global contagion of COVID-19 derives the scientist and clinician to find successful treatments for cure or prevention of severe infection. So far, thousands of clinical trials been performed towards inhibition of viral entry, interference with viral replication and modulation of immune reactions in response to severe COVID-19. The effectiveness of

most of these drugs were not proven yet (ClinicalTrials.gov database of COVID-19 interventional studies). The commonly used drugs in treatment could modify glucose metabolism and//or insulin sensitivity that can further worsening the diabetic patients status in severe infection.

Corticosteroid

The World Health Organization (WHO) adopted the use of dexamethasone as a treatment of sever COVID-19 patients. Dexamethasone use is associated with significant reduction of number of ventilator- free days in patients with severe ARDS in COVID-19 (Tomazini *et al*., 2020) and improve outcome in patients on oxygen therapy without ventilator (Sterne *et al*., 2020). However, it is well reported that the use systemic corticosteroids is associated with different disturbances of glucose metabolism such as; hyperglycaemia, increase insulin resistance and different degree of β- cell dysfunction (Bonaventura & Montecucco, 2018). As we stated earlier, that hyperglycemia could be an independent predictor for worsening outcome in sever COVID-19, and prescribing of systemic corticosteroids can worsen the hyperglycemia. Thus, the decrease in mortality reported with corticosteroids administration can be constricted due to its hyperglycemic effects.

IL-6 receptor antagonist

Tocilizumab drug is a biological mediator acting by binding to IL- 6 receptor leading to interference of signalling pathway of IL- 6 and associated with attenuation of cytokine storm phenomena of severe COVID- 19 (Sanders, Monogue, Jodlowski, & Cutrell, 2020). In treatment of rheumatoid arthritis patients who have diabetes, tocilizumab shown to improve glycemic control by reducing HbA1c through insulin sensitivity improvement (Otsuka *et al*., 2018). The effects of IL- 6 on glucose metabolism and insulin sensitivity are complex. In one hand, inhibition of IL-6 signalling improve insulin signalling and sensitivity. Contrary, chronic IL-6 elevation represents a compensatory mechanisms to increase glucose uptake into skeletal muscle and the use of IL-6 inhibitor could interfere with glucose uptake and further worsening of glycemic status (Jiang, Duque-Guimaraes, Machado, Zierath, & Krook, 2013). In a study performed in Italy, Tocilizumab use failed to decrease risk of COVID-19 progression in hyperglycaemic compared to hyperglycaemic patients (Marfella *et al*., 2020). Thus, the usage of this agent should be further elucidated upon diabetic subjects.

Protease inhibitors (Lopinavir–ritonavir)

These drugs are previously used for treatment of AIDS virus via its protease inhibition activity that impair virus ribonucleic acid processing (Sanders *et al*., 2020). These drugs were shown to markedly increase insulin resistance and decrease glucose uptake causing obvious hyperglycemia (Woerle *et al*., 2003). The efficacy of use of these drugs in severe COVID-19 is under controversy. Both improve outcome (Yan *et al*., 2020) and limited beneficial efficacy (Dalerba, Levin, & Thompson, 2020) are reported in patients with severe COVID-19.

Antivirus drug (Remdesivir)

Remdesivir is a broad-spectrum antiviral medication shown to improve the clinical outcomes of more than half of treated COVID-19 patients (Grein *et al*., 2020). This drug causes an increase in serum glucose in 7% of treated COVID-19 patients due to its hepatic insulin resistance effects and hepatotoxicity (Y. Wang *et al*., 2020). Therefore, using of this antiviral drug could further deteriorate hyperglycemia and precipitate added worsening of severity of COVID-19 diabetic patients.

CONCLUSION

COVID-19 and diabetes mellitus represent a two interacted pandemics. Both conditions affect each other and patients with diabetes subjected to have severe COVID-19 and with increasing risk of mortality and worsening outcome. The most obvious factors interacting in COVID-19 and diabetes are hyperglycemia, inflammation and ACE2 expression and function. Diabetic persons should take a great attention to keep their glycemic control as ideal as possible and put them in the high priority list for gaining vaccination against COVID-19 virus to break the vicious circle of diabetes- COVID-19 interaction.

Consent for Publication

We give the Publisher the permission of the Author to publish the Work.

Disclaimer

The work presented in this review is our own work and not been submitted previously to any other place.

Conflicts of interest

We have no potential conflicts of interest relevant to this article.

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