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Review Article

Impact of SARS-CoV-2 on Onset of Diabetes and Associated Complications

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Abstract

Today, diabetes mellitus and COVID-19 are major worldwide health issues. After several researches, it has been concluded that patients already having diabetes have more chances to be affected by coronavirus. Human pancreas has been suggested as a target of SARS-CoV-2 and it is also suggested that beta cell infection could contribute to the metabolic dysregulation observed in patients with COVID-19. Taken together, our review data indicate that a COVID-19 infection can cause major prolix health problems, like lung damage and even can cause sudden onset of insulin-dependent diabetes. Here in our review article, we have listed case reports along with the mechanistic review of molecular interactions and immunomodulation. Our review has brought out the relation between glucose lowering drugs and COVID-19 and major studies about inflammation and insulin inflammation.

Keywords: COVID-19; Diabetes; SARS-CoV-2

1. Introduction

The epidemic of COVID-19 was caused by SARS-CoV-2 virus in December 2019. The initial cases were from Huanan South China Seafood Market where birds, snakes and bats were sold. It was first thought that it is animal to human transmission and further human to human transmission [1]. It has now spread worldwide and is said to be global pandemic now. SARS-CoV-2 belongs to beta-coronavirus family, it is calculated to be seventh known coronavirus to infect humans on a large scale [2]. Four of these coronaviruses slightly symptomize the patient with cold and chills. Contrarily, the other three, which also include SARS-CoV-2, cause severe symptoms and are fatal, with fatality rates of 10%, 37% and 5% respectively [3]. Although a large number of studies and clinical tests are being launched on COVID-19 in the world, no proof from randomized clinical tests has shown that potential therapy improves outcomes in patients [4]. The virus is expanding at a higher level, at it is getting necessary to bring out any treatment for it. For this, drugs, acids, bases and many other sources are being experimented to bring out proper vaccination for SARS-CoV-2.

SARS-CoV-2 is a single-strained RNA enveloped virus [5]. An RNA based metagenomic next generation sequencing approach has been applied to characterize its entire genome, which has a length of 29,881 bp and encodes almost 9860 amino acids [6]. The fragments of gene express the structural and non-structural proteins. The S, E, M and N genes encode structural proteins while the non-structural proteins are encoded by the ORF region [7]. The surface of SARS-CoV-2 is covered by a variety of glycosylated S protein which bind to the host cell receptor angiotensin-converting enzyme 2, which mediates the entry of viral cell. Once the virus enters the cell, viral RNA is released, polyproteins are translated from the RNA genome, and replication of the viral genome occur along with transcription via protein cleavage and assembly of the replicase-transcriptase complex. Structural proteins are synthesized, assembled and packaged in the host cell and the Viral RNA is replicated [8]. Coronavirus mostly cause gastrointestinal infections or in the respiratory tract. Gamma and delta-coronavirus affect birds while beta and alpha-coronavirus are found in mammals. Today, many researches have come forward regarding relation of coronavirus with other popular diseases.

1.1. Does COVID-19 induce diabetes?

Angiotensin I Converting Enzyme 2 (ACE2) is expressed in key metabolic organs and tissues with endothelial cells such as pancreatic beta cells, the heart, and the kidney [9]. As ACE2 is the major cell entry receptor for SARS-COV-2 [10]. The Virus binds with the ACE2 receptor of Beta cells in the pancreas [11]. The immune system mistakenly turns on autoimmune attack after a viral infection and destroys the body's beta cells. The function of Beta cells is to produce a hormone, insulin, that helps control body sugar and use it for energy fuel. But SARS-CoV-2 damage islets and lead to cell injury and apoptosis causing insulin deficiency and hyperglycemic state [9] process similar to type 1 diabetes. Type 1 Diabetes Mellitus (T1DM) is an autoimmune chronic disease in which pancreatic β-cell loss results in insulin deficiency and leads to hyperglycemia [12]. Coronavirus infections are known to cause diabetes [11] diabetes type1 or maybe a new set of diabetes.

1.2. SARS-CoV-2 and diabetes

COVID 19 is severe respiratory syndrome which belongs to family of viruses and is caused by SARS-CoV-2, an enveloped single stranded RNA virus which belongs to the coronavirus family [13]. The escaped from China and is considered a serious global threat by WHO. The virus enters the lungs through the respiratory system and then enter the alveoli and here it penetrates to host by protein of virus [14]. The RNA of virus uses host cell enzyme RNA polymerase to replicate itself and ultimately increases its number inside the host cell [15]. Diabetes mellitus hyperglycemia is basically a metabolic disease caused by abnormal insulin secretions or action; it is an international health threat. Diabetes type 1 T1DM is basically autoimmune diabetes that is caused due to the pancreatic B cell [16]. Diabetes type 2 T2DM is caused due to the resistivity action of insulin.

1.3. How SARS-CoV-2 cause diabetes?

As COVID-19 is a global pandemic it is reported that people having certain health issue are at greater risk of affecting from SARS-CoV-2. Diabetes is among one of the diseases which increase the rate of infection among COVID-19 patients [17]. Studies have revealed that angiotensin-converting enzyme 2 (ACE2) is responsible for the entrance to host i.e., SARS COV 2 in the body of diabetic patient via pancreatic endocrine cells [18].

2. Observational Literature Review

Recent researches on the topic under-discussion conclude that diabetes surely has an impact on clinical outcome. It has been reported that the predicting factor for unfavorable clinical outcome is diabetes [19]. Different studies have revealed the relationship of COVID-19 with diabetic patients. An other study has shown that out of 355 COVID-19 patients 126 died, in which 35.5 % patients were diabetic and other 0.8 % have no trace of diabetes [20]. Wu studies revealed that the rate of death of COVID-19 patients was 7.3% which is higher than 2.3% i.e., overall death rate (21). According to Guan's study diabetes prevalence was seemed to be higher in severe patients 28 out of 172 (16.2 %) than non-severe patients 53 out of 926 (5.7%) [22]. Same in Wang's study in which diabetes prevalence 15.8 % in severe patients (43/274) than non-severe patients in which ratio was 17.2 % (11/65) [23]. Data was also concluded on basis of ARDS which showed that diabetes prevalence was higher in ARDS patients i.e., 20.8 % (11/53) than non-ARDS 1.8% (1/56) [24].

2.1. Potential Molecular Mechanisms

Potential molecular mechanisms about why patients with DM are at a higher risk of severe COVID-19 than infected individuals without DM. In the association between DM and COVID-19, the role of ACE2 is plausible. In normal conditions, ACE2 performs the function of disintegration of angiotensin-II and to a lesser extent, angiotensin-I to smaller peptides, angiotensin [1-7] and angiotensin [1-9], respectively [25]. ACE2/ANG [1-7] system plays a very significant anti-oxidant and anti-inflammatory role protecting the lungs against ARDS; indeed, against lethal avian influenza A H5N1 infection, ACE2 has been shown to be very protecting and defending [26]. In diabetic patients the expression of ACE2 is reduced due to the reason of glycosylation; this might explain the increased predisposition to severe lung injury and ARDS with COVID-19 [25]. In this situation the role of ACE inhibitors and angiotensin-receptor blockers (ARBS) is very crucial. These are the drugs that are generally and widely used in DM. In diabetic patients the

expression of ACE2 is increased on Ace and ARBS as an adaptive response in order to counteract and oppose raised levels of Ang-II and Ang-I [27]. So, using ACE2 -stimulating drugs would make easy and facilitate the entrance of SARS-COV-2 into pneumocytes and it led to more critical and fatal disease [27] High prevalence of hypokalemia has been shown in critically ill patients with COVID-19 as a result of renal potassium wasting [28]. This is due to the reason of downregulation of ACE2 following viral intrusion which results in decreased degradation of angiotensin-II, increased secretion of aldosterone and consequently increased urinary loss of potassium [28]. So, over-expression of ACE2, while allowing and facilitating the entrance of SARS-COV-2, is unable to provide protection to the lungs against injury as the enzymes gets broken-down by the virus [29].

2.2. Inflammation and activation of immune system

DM has association with chronic low-grade inflammation in the body and diabetic patients have higher circulatory levels of cytokines [30] and these cytokines are involved in the pathophysiology of various diabetic complications and increase the risk of diabetes-induced tissue damages [31]. COVID-19 is characterized by storms of inflammatory responses and higher levels of circulatory cytokines and it is demonstrated that the patients of COVID-19 have impaired immune system activity especially with critical illness [32]. Due to existence of chronic inflammation in DM, it could be a reinforcer of inflammatory responses and increase the risk of inflammation storms in COVID-19 patient (33). Guo et al. estimated 174 patients with confirmed COVID-19 and found that in patients with diabetes the levels of various inflammatory cytokines including interleukin-6 (IL-6), C-Reactive Proteins (CRP), serum ferritin, coagulation index, and D-dimer were significantly higher than nondiabetic COVID-19 patients and his finding suggests that patients with DM are more susceptible to inflammatory storms leading to more severe and critical degrees of the respiratory infections [33].

2.3. ER Stress and COVID-19 induced Diabetes

In ordered to maintain cellular homeostasis, ER shuttles the biomolecules to their correct target and destination [34]. In these activities the resident chaperons of ER, GRP78 (glucose-regulated protein 78) and GRP94, play remarkable and significant role [35]. Any kind of impairment in the activity of ER is related to the aggregation of un/misfolded protein in the lumen of the ER and it results in a pathologic state and condition of “ER stress” [36]. Upon development of ER stress Unfolded Protein Response (UPR) is triggered and activated for the maintenance of homeostasis in the cells [37]. In the diabetic milieu ER stress is the common event and it has closely linked to various complications that have association with diabetes [38] and on the other hand it has very powerful and influential interactions with the activity of corona virus [39]. It is proved that corona viruses induced ER stress by upregulation of spike proteins and promotes virus’s cellular entry [40]. Additionally, it was suggested that ER stress promotes and facilitates the replication of virus and infection of corona viruses and it also raises the pathogenicity of these viruses [41]. The upregulation of GRP94 and GRP78 chaperons occurs by the cells overexpressing S2 subunit of SARS-CoV-2 spike [42]. Also, in murine cells infected with SARS-CoV-2, other biomarkers of ER stress like HERPUD1 (homocysteine-inducible, ER stress-inducible, ubiquitin-like domain member 1) were upregulated

[39] and it indicates that ER has a very important role in pathogenicity of the coronaviruses [40]. SARS-CoV-2 have the ability of modulating different molecular pathways that are involved in the UPR, such as PKR-like ER protein kinase, PERK, Eukaryotic Initiation Factor 2 (eIf2-α) phosphorylation, inositol-requiring protein-1 (IRE1), and activating transcriptional factor-6 (ATF6) [37]. It can be speculated that SARS-CoV2's pathogenicity in patients having DM has a linked to preexisting ER stress in these patients which might encourage and promote entry of virus and pathogenicity [42].

2.4. Oxidative Stress and SARS-CoV-2 induced Diabetes

The imbalance between free radical species and the potency of antioxidant defense systems in favor of the free radicals is referred as oxidative stress and it plays a crucial role in the pathophysiology of various complications of DM as well as viral respiratory disorders [43]. It has been shown that DM has an association with the procreation of excess free radicals [44]. Uncontrolled DM induces oxidative stress through at least ten molecular mechanisms [44] & this oxidative milieu is implicated in most of the viral infections and may lead to increase of the pathogenicity of viruses like coronaviruses [34]. It is one of the main factors helping and aiding coronavirus replication in the host cells [34] and moreover it activates other pathophysiologic pathways such as necrosis and inflammation and promotes downstream molecular mechanisms such as Mitogen-Activated Protein Kinase (MAPK) which is responsible for intensifying and boosting the progression of viral infection in the tissue [42]. Oxidative stress may facilitate and helps the entry of coronavirus into the cells by modulating their route of entry [42]. For example, free radicals have significant and an important impact on the transmembrane protease serine 2, a primary protein which is involved in non-endosomal entry of virus, and alter its distribution [45]. So, in host cells, oxidative stress is an important determinant and deciding factor for the entrance, replication, and pathogenesis of coronavirus [46]. It is reported that risk of corona virus infection increases due to oxidative stress and it was demonstrated that G6PD (glucose-6-phosphate dehydrogenase) deficient cultured cells are more susceptible to coronavirus-induced infection as compared to normal cells [10]. G6PD is a crucial metabolic enzyme which is involved in the maintenance of normal cellular redox state.

2.5. Glucotoxicity and COVID-19 Associated Diabetes

The toxic effect of surplus and excess amount of glucose on various metabolic pathways, which is often seen with uncontrolled DM, is called as glucotoxicity [47]. In hyperglycemic milieu this pathologic process deranges and unbalanced the glucose homeostasis [47]. Glucotoxicity has very crucial indirect roles in hyperglycemia-dependent histological damages in various types of tissues including the respiratory tract and the lungs [48]. It has been suggested that COVID-19 induces tissue injuries in the diabetic milieu has an association with the glucotoxicity which has the ability of stimulating and promoting other pathophysiologic mechanisms [48]. It has been reported by Codon and coworkers that upraised level of glucose promote COVID-19 infections by a hypoxia-inducible factor-1α- (HIF-1α) dependent mechanism [49].

2.6. Immuno-Modulation Due to SARS-CoV-2

Due to SARS-COV2 infection, alteration and modification in the immune system of human body is

called immune-modulation of SARS-CoV-2. Coronavirus enhances blood (plasma) glucose level that further leads to diabetic risks factors in COVID-19 patient's body [50]. That leads to disturbance in cytokine release from macrophages and from T-cells [51]. Being a COVID-19 victim, innate immune responses are also altered in diabetic patients. Those covid-19 patients suffering with high blood glucose level also face low CD4+T cells counts as well as TH17 cells counts [52]. Age factor and diabetes both imparts a serious T and B cells disorder of immune system. These cells do not work properly after coronavirus sufferer and that results in decreased immune capability against viral infection [54]. Impaired immune responses and diabetic disorders collectively increase duration and severity of COVID-19 and weaken our immune system. Through proper focus on human biology about diabetic severity and immune-modulation, we can conclude that this condition badly affected our CD4+T cells and CD8+T cells count. It weakens our immune system response and reduces cell-mediated immunity. This leads to bad effects on health progress of COVID-19 patient.

2.7. Inflammation and Insulin Resistance

Inflammation is a natural defense response of our body against any pathogen or virus. When there is an exposure of target cells to the defective insulin then the condition of insulin resistance occurred [55]. Due to increased blood glucose level after COVID-19 insulin resistance is a common issue of patients. Inflammation and insulin resistance are co-related terms. Due to COVID-19, first our body cells resist and cause inflammation. After inflammation, temperature rises, other body symptoms also appeared including increased hyperglycemia. This further leads to excess defective production of insulin in blood rather than healthy insulin. That excess defective insulin when exposed to healthy body cells, it will affect cells functioning and defect it [56].

2.8. Glucose Lowering Drugs and COVID-19

Glucose-lowering medications unremarkably want to treat diabetes might need effects on COVID-19 pathological process, and these effects might have implications for the management of patients with diabetes and COVID-19 [56]. Glucose-lowering medication employed in the treatment of patients with polygenic disorder might need vital effects on COVID-19 pathophysiology, probably touching the chance of progression to severe malady and mortality. In The Lancet polygenic disorder & medicine, Kamlesh Kunti and colleagues report COVID-19 mortality rates for patients with sort two polygenic on totally different glucose-lowering therapies, in associate empiric nationwide study in European country [57]. The pre-infection prescription of glucose-lowering therapies and risk of COVID-19 mortality was analyzed in 2.85 million individuals with sort 2 polygenic disorder, covering virtually UN agency the entire population of individuals with sort two polygenic disorder who were registered with a general observe in European country irrespective of whether or not or not patients had been admitted to hospital. Overall, a COVID-19-related death occurred in 13,479 (0.5%) of the 2,851,465 patients throughout the study amount [58]. Metformin, SGLT2 inhibitors, and sulfonylureas were related to reduced risks of the COVID-19-related mortality, whereas hypoglycemic agent and DPP-4 inhibitors were related to will increase in risk; neutral results were found for GLP-1 receptor agonists and thiazolidinediones [59]. Sadly, information wasn't offered to permit the researchers to spot once the medication were stopped throughout the progression of COVID-19, and it had been

insufferable to ascertain whether or not the mixture therapies that area unit wide wont to management polygenic disorder in European country had any result on mortality [60].

2.9. Symptoms Shown by The Patients with Both Diabetes and COVID-19

COVID-19 is a contagious disease. Patients having COVID-19 show the main signs of fever, dry cough, fatigue, and dyspnea [61]. A COVID-19 patient would face other complications like acute respiratory distress syndrome, abnormal clotting, sepsis, acute heart damage, secondary infections, damages to the liver, and kidneys [62]. A common metabolic disease called Diabetes mellitus can down-regulate the immune system [63] showing classic symptoms such as frequent urination, an increase in thirst, and a rise in appetite in both type 1 and type 2 diabetes with the development of severe hyperglycemia and high levels of hyperglycemia respectively [64]. In 2020, a statement was reported in the International Diabetes Federation (IDF) that symptoms shown by diabetic patients are not different from other COVID-19 patients [65]. According to case-report study, Fever (38.6 °C), cough, congested pharynx, mild swelling of the bilateral tonsils, coarse breath without rales, decrease of blood oxygen saturation, increased percentage of neutrophils and lymphocytes, decreased total protein and albumin, elevated serum glycated hemoglobin, and elevated ESR and CRP, except blood glucose and glycated hemoglobin, maybe have neither difference with other patients [66]. But there is an agreement that diabetic patients developed more symptoms [67, 68].

3. Conclusion

Individuals with diabetes are at higher risk of having other infections or attacking of virus, and have greater increase in mortality than non-diabetic patients. The potential role of SARS-CoV-2 in inducing diabetes is likely to be more complex than the mere notion of pancreatic ACE2 expression and beta cell destruction. Evidence suggest that insulin and dipeptidyl peptidase 4 inhibitors can be used safely in patients with diabetes mellitus and COVID-19. Choice of glucose lowering, antihypertensive and lipid lowering medications is an important topic for future researches. In series of ICU patients with SARS-CoV-2, a substantial number of patients had hyperglycemia.

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