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Review Article

Covid-19 Induced Diabetes: Disclosing Truth behind the Potential Attention Seeker

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ABSTRACT

Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2), the zoonotic virus answerable for the current global health crisis is ringing its dangerous bells on its post disease status. COVID-19 is causing multiple organ damage probably with its entry site. Insulin-Dependent Diabetes (IDDM) also known as Type I Diabetes is a multifactorial disease that typically occurs as a result of the interaction of genetic, environmental and immunologic factors. The mechanisms behind the development of Diabetes and associated consequences are complicated. The morphological mass of Insulin producing β-cells in the pancreatic islets of Langerhans and the functional status determine plasma Insulin levels. Insufficient Insulin levels may develop as a result of a lack of β-cell function resulting in hyperglycemia and Diabetes. *Angiotensin-Converting Enzyme* 2 (ACE2) receptor, the binding agent which allows Corona virus to enter and migrate to various organs such as lungs, heart, liver, pancreas, and kidneys is assumed to be responsible for this damage. The over expression of ACE2 receptor on pancreatic endocrine cells paves a way for extensive damage to Islets of Langerhans causing Insulin resistance and deficiency. Another common assumption among the researchers and health care professionals are the dreadful relationship shared by viruses and Diabetes which can exacerbate or provoke autoimmunity leading to β-cell auto-oxidation. The metabolic complications like Diabetic Ketoacidosis (DKA) and Hyper osmolar hyperglycemia are predominantly seen in various regions of the world in people with Pre-Diabetes and non-diabetics. However, this review explored the probable truth behind COVID-19 induced new-onset Diabetes mellitus and its complications.

Key words: COVID -19, Type-1 Diabetes, ACE2 receptor, Diabetic, Ketoacidosis.

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INTRODUCTION

The COVID-19 pandemic has been wreaking havoc on the world for the past year and a half, with heart rending morbidity and mortality rates. The virus that caused the corona virus disease pandemic of 2019 (COVID-19) is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] Infection with SARS-CoV-2causes a large range of symptoms, including moderate acute respiratory sickness, respiratory failure, acute respiratory distress syndrome, and septic shock.[2,3] The *Angiotensin Converting Enzyme*-2 (ACE2) receptor located in several human organs acts as a barricade allowing SARS-CoV-2 into host cells.[4] Despite acting as an entry gate to viral particles, ACE2 hydrolyses *angiotensin-II* to *angiotensin* (I-VII) aid in counteracting the deleterious effects of the *Renin - Angiotensin System* (RAS) and exerts anti-inflammatory actions. Various studies have been reported that SARS-CoV-2 infection could down regulate ACE2 expression on cells, thereby disrupting the physiological balance between ACE2 and Angiotensin subsets.[5] Excessive expression of cytokines and chemokines, insufficient interferon response, excessive recruitment of inflammatory cells and possible auto-antibody production are all thought to be significant considerations in disease pathogenesis induced by viruses.[6] Plasma levels of pro-inflammatory cytokines (PICs) and *chemokines*, such as *interleukins* (IL-1, IL-6, IL-8, IL-12), *Interferon-gamma-inducible protein* 10 (IP-10) and monocyte chemoattractant protein-1 (MCP-1) are much higher in SARS infected patients.[7,8] Severe disease is more common in older people and people who have underlying medical conditions such as Hypertension, Diabetes, Cardiovascular disease, Chronic lung disease, Cancer and Chronic kidney disease.[9]

Diabetes is considered as one of the essential risk factors for both kinds of Severe Acute Respiratory Syndrome Corona virus infection (SARS-CoV-1 and SARS-CoV-2).[4] Epidemiological studies indicate that the Diabetes is the second common co-morbidity in COVID-19.[4,10] Uncontrolled glucose levels directly or indirectly impact the increased hospitalizations and mortality, especially during these pandemic conditions. It is repeatedly observed these days that COVID-19 and Diabetes are playing a mutual role in devastating the health conditions resulting to be a fatal one by inducing severe metabolic decompositions in Pre-Diabetic and people with new-onset Diabetes. Much pathology is assumed to be the reason for new-onset Diabetes caused by SARS-CoV-2 in the previously non-diabetic populations.[11]

Type 1 Diabetes (T1D) is an autoimmune illness that causes the Insulin producing cells in the pancreatic islets of Langerhans to malfunction and/or dies.[12-16] The Insulin Dependent Diabetes Mellitus (IDDM) is more common in children, although it can also affect adults.[17] The classic onset trio of signs and symptoms associated with type 1 Diabetes are polydipsia, polyphagia, and polyuria along with hyperglycemia remain as diagnostic hallmarks of Type I Diabetes mellitus.[18-20] Environmental factors play a major role in the onset of IDDM which further on interaction with predisposing genes may induce an autoimmune attack on β-cells of the pancreas.[1,4] The β-cell mass and function predominantly play a significant role in estimating plasma insulin levels. Insulin resistance or deficiency caused by impaired β-cell function or insufficient β-cell count respectively may result in hyperglycemia, further leading to Diabetes.[12] The Type 1 Diabetes is characterized histologically by an immune

infiltrate containing significant numbers of mononuclear cells and CD8+ T lymphocytes within or around the pancreatic islets (Insulitis). CD8+ T cells appear to predominate, but the proportion of CD4+ and CD8+ T cells, as well as the importance of other cell types in the infiltrate (e.g., *Natural Killer Cells* (NKC), Macrophages and Dendritic cells) are unknown.[21] The Morphological approaches reveal a significant loss in β-cells over the time indicating a chronic autoimmune inflammation triggered by macrophages and lymphocytes that surround and infiltrate the islets.[22,23] The β-cell autoimmunity is generally acknowledged as a chronic inflammatory response defined by the gradual infiltration of numerous immune effectors into the pancreatic islets.[24,25] The autoimmune response of IDDM is aggravated by a significant genetic link among particular human leukocyte antigen haplotypes, as well as many variants of genes expressed by β-cells, T cells and other immune effectors[26-32] β-cells expressing *Human Leukocyte Antigen* (HLA) class I antigens including peptides from one or more major autoantigens or environmental triggers (e.g., viruses) are hypothesized to be identified by specialized cytotoxic CD8+ T lymphocytes and targeted for destruction.[1,4,21]

Transforming its face, the novel Corona virus continued to be at its peak concentration in various countries by rapidly spreading through symptomatic and asymptomatic transmitters. Despite its direct effects on defeating human health, it is also involved in causing multiple organ damage with unknown pathology.[10] Having a bi-directional link between SARS-CoV-2 infection and poor glycemic control in Pre-Diabetes, hyperglycemia is digging the routes for increased hospitalizations, morbidity and mortality (Figure 1).

PATHOLOGICAL COMPLICATIONS INDUCED BY COVID 19 INFECTION- DIABETES, KETOACIDOSIS AND OTHER IMPAIRED FUNCTIONS

The exact pathophysiology behind new-onset Diabetes among COVID-19 patients is not yet known.[33] Assumptions were made based on the relationship (Figure 2) shared by viruses with Diabetes, the multi organ functional nature of the ACE2 receptor (which is said to be the entry point of SARS-CoV-2) and the β-cells autoimmune response towards inflammatory mediators.[11]

VIRAL INFECTION AND PANCREATIC B-CELLS

It is known for decades that viral infections and Type-1 Diabetes are very much correlated in their pathogenesis. The viruses commonly involved

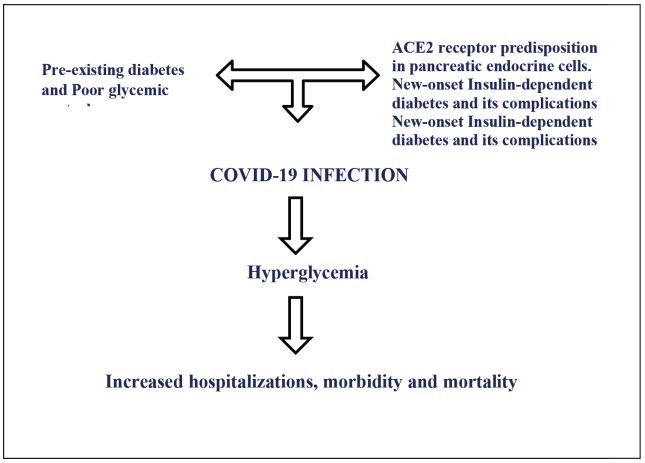

Figure 1: Bi-Directional Link between Covid-19 and Diabetes.

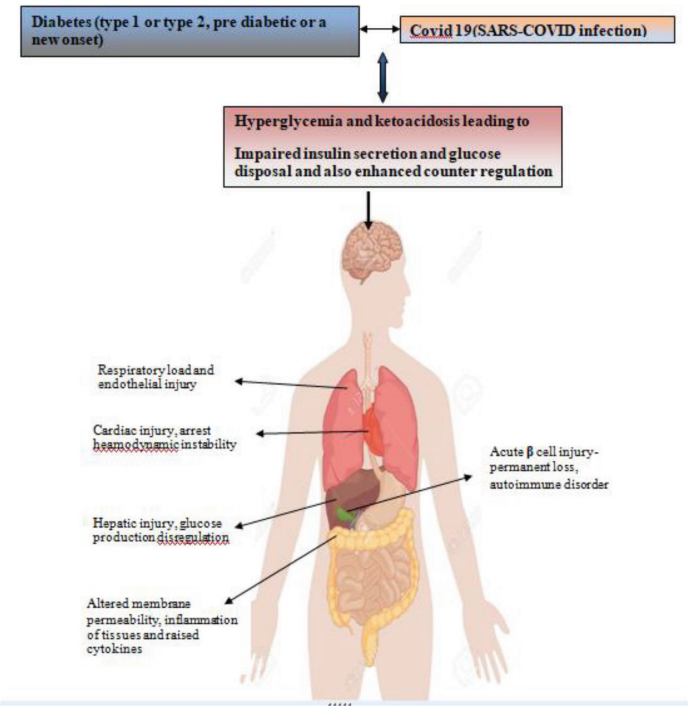

Figure 2: Pathogenesis of Covid-19 Induced Diabetes and ketoacidosis.

in inducing T1D are *Enteroviruses* (EVs), particularly *Cox Sackievirus B* (CVBs). The other viruses which can also cause the development of IDDM are Mumps, Rubella, Cytomegalovirus, *Epstein-Barr* virus, *Rotavirus*.[13,16,24,34-38] In theory, virus-induced beta-cell damage is caused by either direct lytic effects of viral replication or damage mediated by auto reactive CD 4+ T cells in response to the host inflammatory response, resulting in auto immunity. While direct viral infection destroys more than 90% of β-cells, limited lysis releases Islet cell antigens,[19-22] which in conjunction with an augmented immune response leads to autoimmunity.[29-32]

Autoimmune generation is thought to be the plausible explanation for the obliteration of β-cells in the Islets of Langerhans, resulting in low insulin levels and increased glucose levels. Interconnection between SARS-CoV and Diabetes is analyzed in various studies. From the insights of the 2003 pandemic, hyperglycemia was noted as a predictor of morbidity and mortality.[18] Increased glucose levels are detected in mildly infected patients who are not on corticosteroids reflecting a thought shift to the destruction of β-cells hypothesis.[43] A study conducted in 2017 named The Environmental Determinants of Diabetes in the Young (TEDDY) reported that 87,327 patients with a recent respiratory (upper and lower) tract infection were at high risk of developing β-cell autoimmunity. The Corona viruses were detected as one of the pathogens responsible for the infection caused among the subjects enrolled in the study.[24] Pancreatic β-cell annihilation concerning viral diseases can be clarified through different components. The amplification cycle of the virus and/or diffusion of viral antigens through course may straightforwardly bring about loss of β-cells deciding a forceful immune assault involving surrounding pancreatic cells.[25-28] Damage to β-cells may result in the release of islet antigens expressed by antigen-presenting cells in regional lymph nodes. Over expression of the major histocompatibility complex (Class-I) protein could be the reason for the β-cell epitope's prolonged exposure to the immune system, especially in chronic infection situations, allowing for an increased chance of auto-antibody formation. Cross-reactive antibody production against β-cells can be observed even after complete clearance of viral infection through the similar

homologies shared among viral epitopes and amino acid sequences of auto antigens. Predominantly, the release of cytokines and activation of T-cells can contribute to an insulin-dependent Diabetes mellitus through a viral infection generally in individuals predisposed to autoimmunity genetically.[26]

SARS-COV-2 AND ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2)

Angiotensin-Converting Enzyme 2 (ACE2) is thought to be the novel corona virus major binding receptor for causing multisystem damage, and a recent study confirmed that SARS-CoV-2 uses ACE2 as a functional binding receptor.[27,28] ACE2 is primarily linked to cell membranes and is only rarely seen in a soluble form in the circulation. The breakdown of Angiotensin II to angiotensin1-7 is a major beneficial activity of membrane-bound and soluble ACE2. As a result, ACE2 receptors restrict several deleterious effects caused by Angiotensin II binding to AT1 receptors, including vasoconstriction, increased inflammation, and thrombosis.[29] The ACE-2 receptor is part of the RAS's dual system, which includes the ACE-Ang-II-AT1R axis and the *ACE-2-Ang-(1–7)-Mas* axis. The *ACE-Ang-II-AT1R* axis is known to be upregulated in metabolic diseases and with increasing age, while the *ACE-2-Ang-(1–7) Mas* axis is down regulated. In the respiratory system, the activated *ACE-Ang-II-AT1R* axis causes pro-inflammatory and pro-fibrotic effects. It also has the ability to cause vascular dysfunction, cardiac fibrosis, nephropathy, and insulin secretory abnormalities with enhanced insulin resistance upon activation. Initially, it is determined that ACE2 was located abundantly in the small intestine and epithelia of the lungs from all the fifteen homes (organs) in humans. Later, a study conducted on 72 human tissues by harmer and his co-investigators confirmed lung parenchyma, bronchus, ileus, testis, renal, cardiovascular, and gastrointestinal tissues along with pancreas where ACE2 mRNA expression was observed.[31] Twenty out of thirty nine patients with an average age of 47.2 ± 2 years had developed Type-1 Diabetes during their hospital tenure. Only two patients out of six who were discharged with new onset insulin-dependent Diabetes had active Diabetes following a three-year follow-up, indicating that this new-onset Diabetes is transient and may not be lasting.[32]

Various autopsy studies performed to analyze the multi-organ effect of SARS-COVID-19 on patients who faced death due to infection demonstrated few atypical pathology changes which may have contributed to the mortality.[33-35] Fatty degeneration, hydropic degeneration, and interstitial cell proliferation in the heart, liver, pancreas, and kidney were the pathological variations mentioned in those studies.[36] According to a recent study focusing on evaluating pancreatic lesions pathogenesis and glucose intolerance in SARS patients, SARS-CoV can damage several organs, including the lungs, kidneys, heart, and pancreas (particularly the endocrine component). This study also suggested SARS-CoV may cause Acute Type-1 Diabetes relating to its damage on Islets of Langerhans and its abundant expression on endocrine tissues than the exocrine part of the pancreas.[37]

Despite studies demonstrating the independence between corticosteroid administration and hyperglycemia in new-onset Diabetes in active and/or post COVID-19 patients, hyperglycemia is one of the most commonly seen side effects of glucocorticoids treatment.[43] Irrespective of the actual pathway leading to high glucose levels in a non-diabetic person, COVID-19 is the building of its blocks by increasing hospitalizations and mortalities (Figure 2).

COVID-19 AND DIABETIC KETOACIDOSIS (DKA)

COVID-19 patients with pre-existing Diabetes, particularly those with poor glycemic control, had severe metabolic consequences such as Diabetic Ketoacidosis (DKA) and Hyperosmolarity.[38-47] Diabetic ketoacidosis is the most common hyperglycemic crisis involving hyper osmolar hyperglycemia and hyper osmolar ketoacidosis.[44] Deficiency of insulin and insulin resistance caused by viral mechanisms may precipitate ketosis due to impaired glucose use. While there isn't enough data to determine the relation between new-onset DKA and COVID-19, few studies have explored the potential. According to a cohort study, 42 of 658 hospitalized patients with an active COVID-19 infection (mean age: 57.5 years) developed ketosis. Only one of the two active instances of newly formed DKA reported by Nadine and her colleagues had a previous history of Diabetes.[45] According to report by Kulachanya Suwanwongse and Nehad Shabarek 2021, around 15% of patients with active COVID-19 infection and pre-existing Diabetic Mellitus developed DKA, with a 50 percent fatality risk. They also documented three cases of previously non-diabetic patients developing new-onset DKA, two of whom had a family history of Diabetes.[33]

Take Home Message For Researchers And Physicians

Regular monitoring of blood glucose levels and esteemed observation of signs and symptoms of Diabetes and its metabolic complications like DKA is very much necessary to avoid end-stage mortality and morbidity. Further studies should be implicated in exploring the prevention and management patterns of new-onset Diabetes caused by the novel corona virus. The puzzle behind these complications, caused by COVID-19 should be solved as soon as possible which can aid in designing treatment guidelines based on condition and severity. Continuous education of all healthcare professionals regarding day-to-day complications cost by SARS-CoV-2 will help in the betterment of patient care.

CONCLUSION

SARS-CoV-2, the virus that causes COVID-19, has a significant influence on worldwide health. Despite COVID-19's specific disease-causing activities, SARS-CoV-2 is also causing a slew of opportunistic infections and complications, all of which worsen the prognosis. Insulin insufficiency and resistance are thought to be associated with SARS-CoV-2 pathogenesis causing vulnerable complications such as Diabetes and diabetic ketoacidosis. The pathological reason behind this mystery is assumed to be the ACE2 receptor serving as the virus's entry point, beta-cell autoimmunity, and the deadly relation between the virus and Diabetes. But there are not many studies proving this theoretical pathophysiology leading to suppressed insulin levels and increased risk of new-onset Diabetes and its complications. Future research should focus on elucidating the pathogenesis of SARS-CoV-2 that leads to these unique consequences and a poorer prognosis.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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