REVIEW ARTICLE

COVID-19 and the Risk of Diabetes: A Systematic Review Article

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Abstract

Background: COVID-19 pandemic associates with many acute and long-term effects. Hyperglycemia and diabetes are among the common comorbidities that negatively affect the outcome of COVID-19 patients. Many studies report an increase in the incidence of new-onset diabetes and diabetic ketoacidosis during the pandemic of COVID-19.
Aim of the Study: This review article aimed to study the bidirectional relationship between diabetes and COVID-19 and understand the possible underlying mechanisms predisposed to diabetes in patients with COVID-19.
Methods: The present work performs an online literature search on databases from PubMed, Google Scholar, Scopus, ResearchGate, and Web of Science. The search includes publications on SARS-CoV-2 or COVID-19, hyperglycemia, diabetes, and diabetic ketoacidosis.
Results: There is a slight increase in the incidence of hyperglycemia and new-onset diabetes during or post COVID-19 infections. Among the proposed mechanisms of that increase are the direct and indirect effects of SARS-CoV-2 on Beta cells of the pancreas. These effects arise from viral-mediated inflammatory and immunological effects on Beta cells. Stress hyperglycemia, corticosteroid administration, obesity, and preexisting diabetes are important aggravating factors for developing diabetes in COVID-19 patients.
Conclusion: The long-term follow-up is mandatory to determine the outcome of patients, who develop new-onset diabetes after COVID-19 infection.

Keywords: COVID-19, diabetes, diabetic ketoacidosis, hyperglycemia

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INTRODUCTION

The epidemic of coronavirus disease 2019 (COVID-19) started first in Wuhan in China in 2019. The causative agent is the RNA virus associated with severe acute respiratory syndrome, so-called SARS-CoV-2 [1]. After that, it causes a worldwide pandemic [2] and spread all over the world, causing millions of cases and thousands of deaths [3].

The pathogenesis of SARS-CoV-2 is multifactorial, including complex immunological and inflammatory effects in addition to direct viral effects. It has been found that ACE2 receptors play an important role in the disease progression. Therefore, the lungs and other organs with high ACE2 expression are highly invaded by the virus [4].

The S spike protein of SARS-CoV-2 binds with the ACE2 receptor and then enters into host cells to replicate and damage host cells and organs. SARS-CoV-2 enters the host cell by binding ACE2, and this initiates the proinflammatory process that causes the release of cytokines like tumour necrosis factor-alpha (TNFα), interleukins (especially IL-6), and nuclear factor kappa B from infected macrophages. The severe proinflammatory state, called cytokine storm, subsequently leads to cascades of hyperinflammatory response, causing multi-organ injury/failure and death [5].

Many studies tried to find the factors that increase mortality in COVID-19 patients. A meta-analysis shows that the male gender and increased age in addition to the presence of comorbid diseases like diabetes, cancers, hypertension, and other cardiovascular disease, are associated with poor prognosis and increased mortality rate in COVID-19 patients. Diabetes is a common chronic progressive disease that is associated with increased morbidity and mortality. Diabetic patients have a high susceptibility to infection due to low immunity. Therefore, diabetes is common comorbidity that increases the morbidity and mortality of COVID-19 patients [6].

On the other hand, there are reports about an increase in the incidence of newly diagnosed diabetes and its acute complications like diabetic ketoacidosis during or post COVID-19 infection. COVID-19 might associate with increased blood glucose in patients with or without preexisting diabetes [7,8].

However, the type of diabetes induced by the virus is still uncertain. The exact effect of COVID-19 infection on blood glucose levels has yet to be fully understood. Theoretically, COVID-19 virus might cause direct damage to pancreatic B

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cells or indirectly by initiating a cytokine storm. The present study aimed to review whether COVID-19 might associate with increased blood glucose and predisposition to diabetes in previously nondiabetic subjects.

METHODS

The present work performs an online literature search on databases from PubMed, Google Scholar, Scopus, ResearchGate, and Web of Science. The following keywords included in the search for relevant articles ("severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "COVID-19") AND ("diabetes" OR "new onset diabetes" OR "diabetic ketoacidosis" OR "hyperglycemia"). The two researchers (N. K and Z. N) were involved in the search. The references from the related articles were also searched for further information. There are no restrictions on the article publication time or location where the study was performed.

RESULTS

Viral infection and blood glucose control

Blood glucose usually increases during acute illness [9]. It hypothesized that, inflammatory response during infection or acute illness leads to decreased insulin sensitivity by increasing counteracting hormones to increase the availability of glucose in systemic circulation required for immune cell activation [10]. Insulin resistance is also stimulated by Proinflammatory cytokines. Viral infection induces the production of interferon-g (IFN-g), which downregulate the insulin receptor in skeletal muscle. However, this action is likely transient due to a compensatory increase in insulin production. Thus, during acute viral infection, there is a transient decrease in insulin sensitivity in muscles, which subsequently produces hyperinsulinemia and activates antiviral immune cells. This all leads to glucose intolerance in pre-diabetic, especially obese patients. [11].

The reciprocal effect of COVID-19 and blood glucose on each other

Type 2 diabetes is an important comorbid disease associated with COVID-19, especially in severe cases. Many studies show a relationship between severe COVID-19 and glycemic control (blood glucose and/or HbA1c). A Study by Zhang et al. found an increase in blood glucose during COVID-19 infection in previously nondiabetic patients [12]. A meta-analysis shows a significant increase in blood glucose in severe cases of COVID-19 infection compared with mild ones [13].

A single-center study of 184 patients positive for SARS-CoV-2 demonstrates that most moderate and severe cases of COVID-19 had diabetes or metabolic disturbances like obesity and prediabetes and hyperglycemia significantly worse during SARS-CoV-2 infection in those patients [14]. Nearby a meta-analysis found that diabetes is significantly associated with poor prognosis in hospitalized patients complaining of severe COVID-19 infection [15]. Another multi-centered, retrospective study in China, including 7,337 cases of COVID-19, found that 952 patients had preexisting type 2 diabetes, and those patients had a high risk of multiple organ injury and mortality than nondiabetic. In addition, well-controlled blood glucose had significantly low mortality [16]. Another meta-analysis demonstrates that patients with high HbA1c had a high risk for covid-19 mortality [17]. Therefore, many clinicians consider glycemic control as a predictor for COVID-19 risk assessment.

COVID-19 and new-onset diabetes

Several studies indicated that the covid19 epidemic was accompanied by a surge in newly diagnosed cases of type 1 [T1D] and type 2 diabetes [T2D] as mentioned in Table 1. According to a Romanian study, there was a significantly higher rate of newly diagnosed type 1 diabetes in the first half of 2020 compared to earlier years (57.8 vs. 51%, $p < 0.0001$). The authors hypothesize that by inducing pancreatic autoimmunity, SARS-CoV-2 may have contributed to that increase. [18].

Another study from London, U.K report about 30 new cases of T1D; their age ranges from 23 months up to 16 years, 70% present with diabetic ketoacidosis (DKA), and about 15% positive for SARS-cov-2. According to this study, new cases of T1D with onset during pandemics increased by 80% in comparison to prior years. [19]. Further study in Finland found an increase in the number of children admitted to pediatric intensive care units with DKA 6.25 in 2016–2019 and 20 during the pandemic (2020) in addition to a small increase in new cases of T1D during a pandemic; however, all cases were COVID-19 negative. This increase in the incidence of T1D in the latter study was explained by indirect effects like lockdown and healthcare accessibility during the pandemic [20].

Even so, a recently published retrospective-prospective study assesses the number of newly diagnosed both type 1 and 2 diabetes in outpatient clinics in Bosnia and Herzegovina a year before the pandemic and two years during COVID-19 pandemic. The latter study discovered that the number of people, who developed type 1 and type 2 diabetes for the first time, was significantly higher in 2020 and 2021 in comparison to 2019. This suggests that all patients at high risk of developing diabetes and those on corticosteroid therapy might develop the disease few weeks after the acute phase of COVID-19 infection [21].

Another study indicated that for age-adjusted children and adolescents, both types T1D and T2D rose post-COVID-19. [22]. In another study, three cases of patients with no prior history or risk factors for diabetes develop new-onset diabetes during acute COVID-19 infection, and their first presentation is DKA. They remain persistently insulin-dependent several months after their recovery [23]. In retrospective cohort research conducted in Germany; COVID-19 infection was linked to an increased risk for type 2 diabetes. [24].

These results require further confirmation studies. However active monitoring of glucose dysregulation is required during and after recovery from SARS-CoV-2 infection.

DISCUSSION

The possible mechanism of new onset diabetes in people with COVID-19 patients

Many theories have been developed and proposed to

Table1. Studies report new onset diabetes in COVID-19 patients

Reference	Country	Design	Population	Results
Valid A et al[18]	Romania	Retrospective Observational	new cases of type 1 diabetes in children aged 0 to 14 years since 1996.	A marked increase in the incidence of type 1 diabetes in the first year of the COVID-19 pandemic, with 16.9%, from 11.4/100,000 in 2019 to 13.3/100,000 in 2020
Unsworth R et al[19]	U.K	Cross-sectional	new-onset T1D age 23 months to 16 years during the peak of the COVID-19 pandemic.	30 children with newly diagnosed T1D, 5 children were COVID-19 positive
Salmi H et al[20]	Finland	retrospective cohort	New onset T1D during pre-pandemic (2016-2019) and at pandemic 2020	57.75 children had T1D in 2016–2019, compared with 84 in 2020, the children diagnosed in 2020 and all were SARS-CoV-2 negative.
Burekovic A et al [21]	Bosnia and Herzegovina	retrospective-prospective	Outpatient in the year before COVID-19, 2019, and during the COVID-19 infection, in 2020 and 2021.	In 2020, out of five newly discovered type 1, 3 of them overcame COVID-19 infection, and diabetes was detected 3-4 weeks after overcoming COVID-19 infection. And of the 122 types 2 patients, 19 were newly diagnosed, 13 were COVID-19 infected, and diabetes was detected 4-6 weeks after infection.
Guo Y et al[22]	Florida, USA	observational descriptive cohort study	New diabetes cases among individuals <18 years before and during the coronavirus disease 2019 pandemic	Incidence of type 1 diabetes increase from (19.9-32.5) per 100,000 prior to the COVID-19 pandemic to (31.8- 36.3) per 100,000 after March 2020. Type 2 diabetes incidence rates also increase from (10.6 and 14.6) per 100,000 prior to the COVID-19 pandemic to 16.9 per 100,000
Ramos-Yataco A et al[23]	Peru	case series	Case series of three patients, who developed new-onset diabetes while suffering from acute COVID-19 infection	DKA is first presentation in those cases and need insulin therapy several months post-recovery
Rathmann G. et al [24]	Germany	retrospective cohort analysis	35,865 individuals with documented Covid-19 in period (March 2020 to January 2021).	Individuals with Covid-19 showed an increased type 2 diabetes incidence

explain why the frequency of newly diagnosed diabetes rises during acute COVID-19 pandemics, including

1-Beta cell dysfunction

Angiotensin-converting enzyme-2 (ACE2) receptors are the pathway for COVID-19 virus entry into the cells. The ACE2 receptors spread over many tissues and organs other than the lungs. Among these tissues, the gastrointestinal organ like the liver, pancreas and intestine are considered important sites for the ACE2 receptor and, therefore these tissues act as reservoirs for viral multiplication mutation. The extrapulmonary effects of SARS-CoV-2 predispose to poor control of the disease and lead to complications like diabetes [25].

The expression of ACE2 in the pancreatic tissue might be related to pancreatic injury during SARS-Cov-2 [26]. The potential mechanism of pancreatic β-cell dysfunction possibly occurs by many hypothetic mechanisms, including induction of direct cell lysis, inflammation, stimulation of apoptosis, autoimmunity, molecular mimicry, and trans-differentiation [27].

Many studies on pancreatic b cells from autopsy samples of infected individuals with COVID-19 found a viral antigen in pancreatic tissue [28]. An ex vivo study on SARS-CoV-2 infections found multiple sites of pancreatic islet cells were invaded by the virus, which led to stress stimulation and chemokines production induction. This process proposed to decrease insulin expression and increase expression of trypsin1 and glucagon due to stress-induced change in cellular trans-differentiation between alpha and beta cells of the pancreas during COVID-19 infection. [29]. Steenblock et al. found that some pancreatic islets were positive for phosphorylated pseudokinase mixed lineage kinase domain-like protein, which is considered a marker for tissue necroptosis [30].

Other phosphoproteomic mass spectrometry analytical study suggested that islet cell death might occur by direct induction of cell apoptosis by activation of kinase protein called c-Jun N-terminal kinase (JNK)-mitogen-activated (MAPK), which is a signaling for programmed cell death process [31]. Furthermore, other studies from COVID-19-infected non-human primates mention that SARS-CoV-2 indirectly causes B-cell dysfunction through thrombosis and fibrosis endothelium of blood vessels in the pancreas and indirectly leads to new-onset diabetes. Qadir et al. found that pancreatic tissue sections from NHPs had multiple vascular thrombi and generalized fibrosis [32].

Similar observations from COVID-19-infected patients reveal the presence of multiple thrombotic lesions in the pancreatic tissue section [33]. The direct and indirect mechanism of b cell dysfunction caused by SARS Cov-2 infection is summarized in Figure (1).

2-Stress hyperglycemia

Stress hyperglycemia refers to transient hyperglycemia that is routinely diagnosed during acute infection. Stress hyperglycemia is usually reported in non-diabetic patients; however, it can occur in diabetic patients [34]. It is considered a normal metabolic response to stressful conditions like acute infection [35]. The underlying

mechanism is usually related to the action of counter-regulatory or stress hormones like glucagon, catecholamines, cortisol, and proinflammatory cytokines, which increase blood glucose by direct stimulation of glycogenolysis and gluconeogenesis and indirectly by peripheral insulin resistance [36]. Acute severe COVID-19 infection might associate with an elevation of blood glucose, explained as stress hyperglycemia [37].

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However, other studies report a new onset diabetes after infection rather than transient hyperglycemia [38,39,40]. Therefore, long-term follow-up is required for patients, who survive from acute SARS-CoV-2 infection to diagnose the long-term effect on blood glucose.

3-Obesity

During the pandemic of coronavirus, it was found that infection was highly prevalent in patients with diabetes and prediabetes, and a significant number of patients were clinically obese [41]. Obese patients have a higher risk of developing a more severe course of disease with increased susceptibility to COVID-19 complications [42,43].

Obesity is a risk factor for many diseases like cardiovascular disease and diabetes. The immune component within Adipose tissue possesses many inflammatory and anti-inflammatory functions. During viral infection, the inflammatory process aggravated the already activated inflammatory process in obese patients. Obesity is proposed to cause chronic systemic inflammation, insulin resistance, gradual pancreatic beta cell dysfunction, and finally, type 2 diabetes [44]. The low-grade inflammation, likely amplified by acute inflammation caused by COVID-19, leads to more severe disease [45]. This process may indicate that many patients, who present with hyperglycemia or obesity might have undiagnosed preexisting diabetes that gets worse during acute viral infection.

4-Steroid induced in hospitalized patients

Steroids are well-known drugs used for various indications like rheumatoid arthritis, autoimmune disease, multiple sclerosis, and others. The administration of steroids for hospitalized COVID-19 patients was found to be associated with decreased disease complications and mortality [46]. Steroids lead to elevated blood glucose by several mechanisms, like increasing hepatic gluconeogenesis, reducing glucose uptake by muscles and adipose tissue, and increasing insulin resistance [47].

A meta-analysis found that glucocorticoid-associated hyperglycemia or diabetes developed in 32.3% and 18.6%, respectively, of people using steroids during hospitalization with COVID-19 [48]. Another study found that the incidence of diabetes in COVID-19-infected patients, who use steroids was 15.65%, and older patients were at the highest risk [49]. The steroid-induced hyperglycemia might worsen other metabolic abnormalities, especially in old patients with the slow recovery of beta cell function that finally leads to new-onset diabetes in such patients.

CONCLUSION

New onset diabetes might associate with COVID-19 infection. Many underlying mechanisms are proposed,

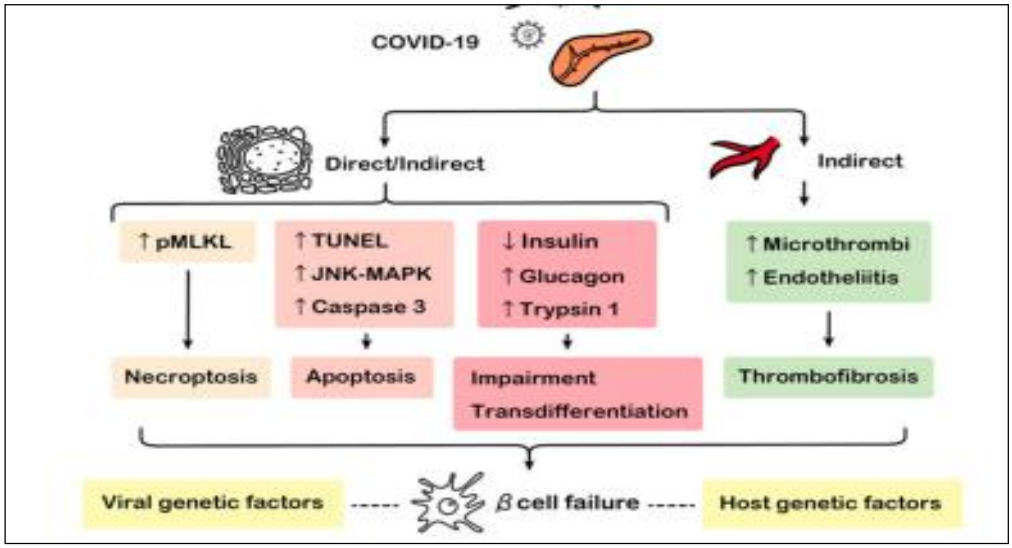

Figure 1. Possible mechanisms of B-cell dysfunction during COVID-19 (27).

including pancreatic beta cell dysfunction via direct viral effect or inflammatory and immunological processes. Stress hyperglycemia, obesity, preexisting diabetes, and steroid administration are aggravating factors for developing diabetes in COVID-19 survivors. However, long-term follow-up is mandatory to determine the outcome of patients, who develop new-onset diabetes after COVID-19 infection.

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