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New-Onset Diabetes Post COVID-19: A Growing Concern

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Abstract:

COVID-19 has been a devastating factor in the recent past times and its associated comorbidities have been evolving over the last few years since the inception of the disease. The emergence of COVID-19 has shed light on a potential link between the virus and the development of new-onset diabetes mellitus (NODM). The relationship between COVID-19 infection and the incidence of diabetes has garnered significant attention and it has been bidirectional. This review article delves into relevant studies published up to March 2023 on the incidence of diabetes post-COVID-19 infection and COVID-19 infection severity in diabetes mellitus patients, exploring the risk factors and potential mechanisms underlying this association, prevention, and management strategies to tackle the associated conditions.

Keywords: New-onset diabetes mellitus, COVID-19, diabetic ketoacidosis, hyperglycemia

Abbreviations: NODM- new-onset diabetes mellitus, DM- diabetes mellitus

Introduction:

After more than two years of the pandemic, a substantial amount of data indicates that SARS-CoV-2 infection can cause post-acute sequelae in a variety of extra-pulmonary organ systems, including the lungs, which are collectively referred to as long COVID. (Aly 2021, Xie 2021). According to the US Centers for Disease Control (CDC) investigation of a sizable electronic healthcare database, those with COVID-19 had a higher risk of developing type 1 and type 2 diabetes at a younger age than those without the virus (353,164 individuals with COVID-19 and 1640776 controls without any signs of infection) (Bull, 2022) . There are a couple of pathways that should be looked into in mechanistic research which are the potential coexistence of (1) COVID-19 causing de novo illness in individuals who might not have otherwise developed diabetes and (2) COVID-19 acting as an amplifier of baseline risks and an accelerator of the disease progression. Researchers from the US Centers for Disease Control and Prevention (US CDC) analyzed two large healthcare databases that suggested that individuals under the age of 18 who contracted SARS-CoV-2 infection had a higher chance of being diagnosed with diabetes during the COVID-19 post-acute phase when compared to non-infected controls. They also demonstrated that COVID-19 was linked to a higher risk of diabetes than pre-pandemic acute respiratory infections and that non-SARS-CoV-2 respiratory infections were not linked to an increased risk for diabetes. (Barrett,2022). The majority of these investigations on COVID-19 and diabetes were carried out before the availability of vaccinations and during a time when reinfections were rare.

Pathophysiology of diabetes and COVID-19: A bidirectional relation

The exact mechanisms by which COVID-19 might trigger NODM are still under investigation. Several hypotheses are explored in the reviewed literature. Direct viral damage to pancreatic beta cells, responsible for insulin production (Gojda,2023, Yang,2010), and inflammation

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caused by the virus (Imai,2008, Chen,2019) are potential contributors. Additionally, COVID-19 may worsen pre-existing insulin resistance through various pathways, including disruption of the renin-angiotensin-aldosterone system (Kuba,2006, Vaduganathan,2020) and increased oxidative stress (Imai,2008). Understanding these mechanisms is crucial for developing preventive and therapeutic strategies.

The prevalence of diabetes in older COVID-19 hospitalized patients raises the possibility that insulin resistance and metabolic decompensation are caused by inflammatory reactions to infection in conjunction with fat. Furthermore, due to their metabolic effects, COVID-19 therapies (e.g., glucocorticoids) may reveal latent diabetes.

Raised glucose levels in human monocytes directly promote SARS-CoV-2 replication, and glycolysis maintains SARS-CoV-2 replication by generating reactive oxygen species in the mitochondria and triggering hypoxia-inducible factor 1α (Codo,2020). Consequently, hyperglycemia may encourage the spread of viruses.

According to research, SARS-CoV-2 may cause hyperglycemia by interfering with fat cells' ability to produce the hormone adiponectin, which aids in blood sugar regulation. In COVID-19 individuals, decreased adiponectin levels may play a role in insulin resistance and hyperglycemia. (Reieterer 2021)

A prospective cohort study showed that patients with severe COVID-19 had increased resting energy expenditure and insulin resistance during the acute phase of the infection and corticosteroid use, but these effects did not persist during the follow-up period of 6 months . Only patients with insufficient insulin response developed hyperglycemia, indicating that beta cell dysfunction, rather than insulin resistance, was responsible for its occurrence. (Gojda,2023)

There are several theories as to how virally-induced inflammation raises insulin resistance. (Sestan,2018) Other inflammatory markers including D-dimer, ferritin, and IL-6 are also elevated in COVID-19 patients (Zhou,2020). These markers may raise the risk of microvascular and macrovascular complications resulting from low-grade vascular inflammation in patients with underlying diabetes mellitus (Cheema,2020). Pro-inflammatory cytokines with a T helper type 1 cell profile are known to raise insulin resistance in obese people (Lee,2014) ; however, it is unknown how these cytokines relate to COVID-19. It's also unknown whether and how SARS-CoV-2 infection affects people who are susceptible to diabetes mellitus in terms of glycaemic control loss. According to one study, an acute respiratory virus infection promotes muscle insulin resistance by increasing the production of IFNγ in humans which drives compensatory hyperinsulinemia to maintain euglycemia and boost antiviral CD8+ T cell responses (Sestan,2018)

It is possible that patients with diabetes mellitus or poor glucose tolerance will not be able to compensate as well. Notably, hyperinsulinemia can directly stimulate the activity of CD8+ effector T cells, hence enhancing antiviral immunity (Sestan,2018) Moreover, hyperglycemia can result from SARS-CoV infection in individuals who do not already have diabetes mellitus (yang,2010) . Together, these data and the location of ACE2 expression in the endocrine pancreas raise the possibility that coronaviruses cause damage to islets particularly, which could result in hyperglycemia (Yang,2010). Notably, hyperglycemia was shown to endure for three years following SARS recovery, which may suggest chronic

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harm to pancreatic β-cells (Yang,2010). . These findings imply that the RAAS's ACE2 may have a role in the link between COVID-19 and diabetes mellitus.

(Alhuthali 2023) discovered that 151 patients (29.4%) were normoglycemic, 77 patients (15%) were pre-diabetic, and 286 patients (55.6%) had diabetes. Regarding the neutrophil count and inflammatory variables of COVID-19 severity, a noteworthy distinction was observed. Additionally, it was discovered that in patients with diabetes and pre-diabetes, the neutrophil count was negatively connected with vitamin D levels and directly correlated with the severity monitoring biochemical markers for COVID-19, including CRP, ESR, ferritin, and D-dimer. The data emphasize the alteration of neutrophils in COVID-19 diabetic and pre-diabetic patients, which was found to correlate negatively with 25(OH)D and positively with CRP, ESR, ferritin, and D-dimer. However, more extensive research is needed to determine how these changes relate to the clinical presentation of the disease.

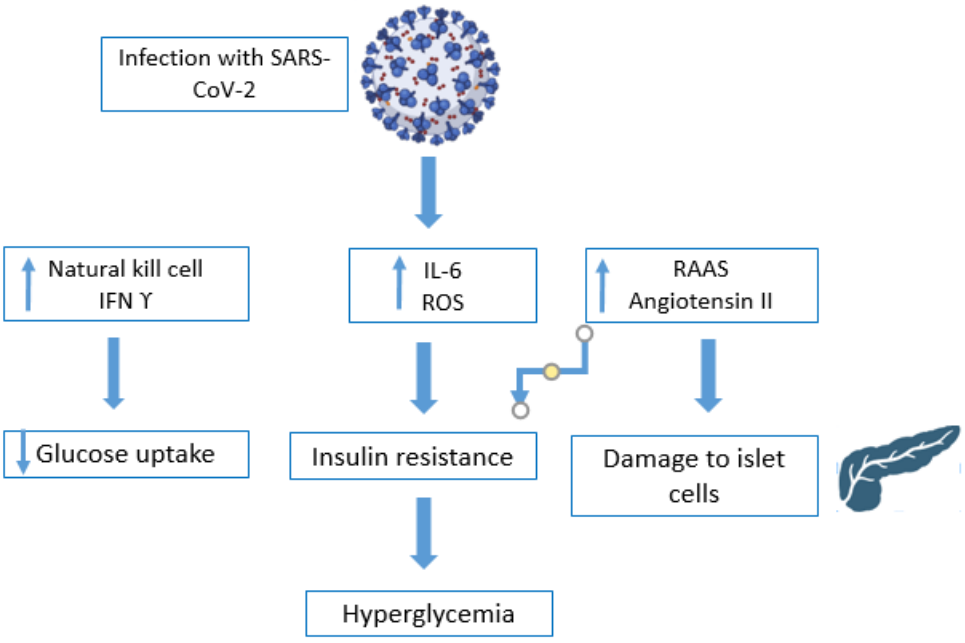

Fig 3: A Plausible mechanism of T2DM onset post-COVID-19: Infection with SARS-CoV-2 leads to increased reactive oxygen species (ROS) production (Teuwen,2020) . ROS production and viral activation of the renin–angiotensin–aldosterone system (RAAS) (Vaduganathan ,2020, Kuba,2006) (via increased angiotensin II expression) cause insulin resistance (sestan,2018) , hyperglycaemia (Critchley,,2018). increased production of IFNγ and activated NK cells exacerbate systemic inflammation in muscle and adipose tissues, overall establishing a detrimental effect on glucose uptake (Wensveen,2015)

Incidence of new-onset diabetes mellitus post- COVID-19:

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In comparison to influenza, a retrospective study examined the rates and risk variables of new-onset persistent type-2 diabetes during COVID-19 hospitalization and at 3-month follow-up. The Montefiore Health System in the Bronx, New York, was home to 8216 hospitalized, 2998 non-hospitalized COVID-19 patients, and 2988 hospitalized influenza patients without a history of pre-diabetes or diabetes. It was found that patients with I-DM (ie, new-onset in-hospital type-2 diabetes mellitus) on COVID-19 were older, more likely to be male, receiving steroid treatment, and had more comorbidities than those without I-DM. This study showed that 16.7% of patients hospitalized for COVID-19 who had no prior history of pre-diabetes or diabetes had new-onset type-2 diabetes at follow-up (3 months). During hospitalization, patients with COVID-19 had an incidence of new-onset diabetes 3.96 times (adjusted odds ratio) higher than patients with influenza. After being admitted to the hospital, older male patients with significant comorbidities were more likely to develop new-onset diabetes. (Justin,2023) . Increases have been noted in the few studies that have looked at incidence rates during the pandemic, albeit rates have varied between investigations. For instance, a multiregional study conducted in a Florida-based health network showed that the age-standardized rates of type 1 and type 2 diabetes, among those under the age of 18, ranged from 19.9-32.5 per 100,000 PYs and 10.6-14.6 per 100,000 PYs, respectively, prior to the pandemic and increased to between 31.8 and 36.3 per 100,000 PYs (type 1 diabetes) and 13.1 to 16.9 per 100,000 PYs (type 2 diabetes) during the pandemic. (Guo, 2022) In contrast, a cohort study that included participants aged from birth to 19 years with no history of diabetes from Kaiser Permanente Southern California (KPSC) between 2016 and 2021 observed that the incidence of type 2 diabetes increased more sharply during the pandemic than that of type 1 diabetes overall, especially among those aged 10 to 19 years. However, since there were comparatively few type 2 diabetes patients among those under the age of nine, the data has to be interpreted cautiously. These variations might be linked to case definitions of incident diabetes or demographic composition, such as youth in the South versus the Southwest of the United States. Some variation in incidence over the study period may also be explained by changes in the underlying denominator populations or changes in the pandemic-related care-seeking behavior. Nevertheless, the results of this study were only little affected when corrected for use before the onset of diabetes. The baseline clinical features of individuals with incident type 1 and type 2 diabetes in this study did not differ between the non-pandemic and pandemic years. Type 1 diabetes increased from 19.55 (95% CI, 16.79-22.31) per 100,000 PYs in 2016 to 24.27 (95% CI, 21.27-27.28) per 100,000 PYs in 2021, according to age- and sex-standardized incidence rates. Similarly, from 15.66 (95% CI, 13.25-18.08) per 100,000 PYs in 2016 to 29.44 (95% CI, 26.19-32.69) per 100,000 PYs in 2021, the age- and sex-standardized incidence rates for type 2 diabetes increased. Comparing 2020–2021 with 2016–2019, the incidence rate of type 2 diabetes increased by 62%. Incidence rates of type 2 diabetes were also greater in 2020–2021 compared to 2016–2019 among individuals aged 10–19 years with females (IRR, 1.44; 95% CI, 1.22-1.69) and males (IRR, 1.83; 95% CI, 1.54–2.17), and Black people (IRR, 1.95; 95% CI, 1.41-2.68). (Mefford 2023)

Individuals less than 18 years of age during 30 days post-COVID-19 and those with prepandemic acute respiratory infections had a higher risk of developing diabetes mellitus which was not associated with any non-SARS-CoV-2 respiratory infections. This study highlights prevention strategies like immunization against COVID-19 in children and

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adolescents as well as emphasizes the significance of keeping an eye on newly diagnosed diabetes following SARS-CoV-2 infection (Catherine,2022)

The necessity of monitoring glucose metabolism during the post-acute phase of COVID-19 is highlighted by a meta-analysis that found a 1.17-fold greater incidence of diabetes among patients with the infection compared to those without it (Zhang et al, 2022). In 8 studies totaling 4,270,747 COVID-19 patients, a systematic review and meta-analysis of the evidence synthesized for COVID-19 and new diabetes was conducted. The results showed that COVID-19 was linked to a 66% increased risk of new-onset diabetes (sentongo 2022) (risk ratio, 1.66; 95% CI 1.38; 2.00). Neither age nor sex nor the quality of the study altered the risk. Another study used the US Department of Veterans Affairs databases for cohort study which examined post-acute risk and burden of incident diabetes in COVID-19 survivors. The study found excess burden of diabetes and anti-hyperglycaemic use in COVID-19 survivors. Risks and burdens of post-acute outcomes were linked to COVID-19 severity.

During the pandemic, the yearly incidence of type 2 diabetes increased by approximately three times compared to previous times, with a 61% increase in the second year compared to the first. During the pandemic, BMI rose in comparison to before (129% of the 95th percentile vs. 141%, $P = 0.02$). Patients had a higher incidence of diabetic ketoacidosis and/or hyperglycemic hyperosmolar syndrome (20% vs. 3.5%, $P = 0.02$) in the first year of treatment compared to previously, and they were comparatively younger (12.9 years vs. 14.8, $P < 0.001$). To prevent delay in diagnosis and to help shape the educational initiatives aimed at countering the pandemic's ongoing effects on health outcomes, providers should be aware of the rising prevalence of type 2 diabetes in young people. (Sabitha 2022)

Data regarding the onset of Type I diabetes mellitus post COVID-19 is scarce considering the higher prevalence of type II diabetes mellitus. A retrospective multicentric study involving 997 type 1 diabetic children and adolescents hospitalized in Turkey's 27 pediatric intensive care units between the start of the pandemic and the year before. During the COVID-19 pandemic, a greater proportion of children with Type 1 diabetes had started showing signs of the disease had DKA ($p < 0.0001$). Additionally, there was a significant increase in the incidence of severe DKA during the COVID-19 pandemic ($p < 0.0001$) and among children who had recently developed Type 1 diabetes ($p < 0.0001$). During the pandemic, there were notable increases in HbA1c levels, longer stays in the intensive care unit, and longer insulin infusion periods. At admission, nine patients tested positive for severe DKA, eight patients tested positive for Type 1 diabetes with a recent onset, and eleven patients tested positive for SARS-CoV-2. The incidence of severe cases and newly diagnosed Type 1 diabetes in children with DKA in the first year of the COVID-19 pandemic. (Kiral,2022)

Case descriptions have shown individuals with newly diagnosed T1DM who experienced ketoacidosis at the outset of COVID-19, as well as those with newly diagnosed T1DM who did not experience ketoacidosis but developed ketoacidosis a few weeks after appearing to recover from COVID-19. On the other hand, specialized hospitals in northwest London, UK, reported a greater than expected number of patients presenting with severe ketoacidosis, suggesting a potential increase in the number of patients with new-onset T1DM (Unsworth,2020). Another study found a statistically significant increase in both diabetic ketoacidosis and severe ketoacidosis in children and adolescents with new-onset T1DM (Kamrath,2020)

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A prospective observational study involving 273 COVID-19-positive individuals was carried out in a tertiary care hospital in India. The study's findings revealed that factors such as a positive family history of diabetes mellitus, a higher body mass index, the duration of the condition, and the dosage of steroids significantly influenced the incidence of new-onset diabetes mellitus at the 3-month mark. Nearly 67% of the patients who developed new- onset pre-diabetes had shortness of breath as the common symptom at the time of admission. (Keerthy , 2022)

The risk of diabetes in the post-acute phase of COVID-19 was not significantly different in people who had a SARS-CoV-2 infection after vaccination than in unvaccinated individuals, according to recent evidence from a US Department of Veterans Affairs study involving over 13 million individuals. Both unvaccinated and vaccinated individuals with SARS-CoV-2 infection are at increased risk of diabetes compared with non-infected controls. (Aly,2022)

Recent observational data from the Nellore government medical college had seen the incidence of new onset of diabetes in a total of 130 patients out of 2600 patients (5%) who were observed for one year between April 2020 to April 2021. The patients had no prior history of prediabetes, type I/II diabetes mellitus. Around 2% of the study population developed new onset diabetes mellitus at the end of the first six months post- COVID-19 presentation which was confirmed through RT-PCR.

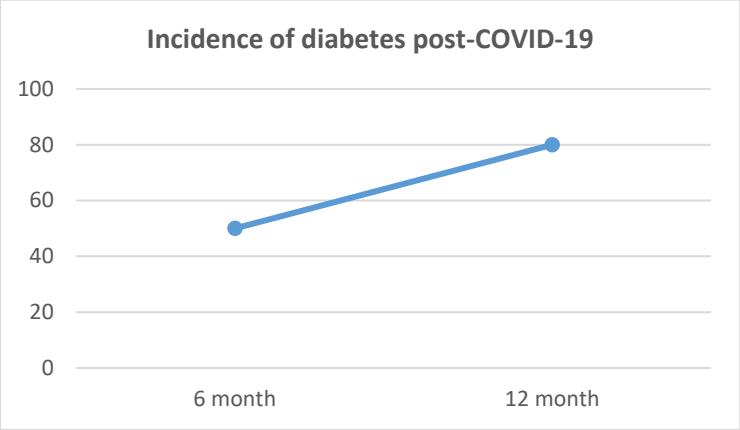

Fig 1. Incidence of new-onset diabetes mellitus post-COVID-19

COVID-19 severity associated with diabetes mellitus:

It is commonly known that individuals with pre-existing diabetes experience a more severe clinical course of SARS-CoV-2 infection (Al Aly,2022). Individuals diagnosed with diabetes mellitus usually have greater SARS-CoV-2 infection severity than people without the disease (Carey,2018 , Wu,2019) and poor glycaemic management indicates a higher risk of medication use, hospitalizations, and fatality. For instance, SARS-CoV infection was linked to a sharply rising requirement for high doses of insulin (sometimes approaching or exceeding 100 IU per day) in patients requiring the drug (Wu,2020). Inflammatory cytokine levels appear to be correlated with changes in insulin requirements (Gianchandani, 2020, Wu,2020). According to a systematic analysis, T2DM was present in 77% of COVID-19 patients who experienced ketoacidosis (Pal,2020) . Microvascular and macrovascular complications of diabetes mellitus

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were strongly associated with an elevated risk of death in patients with COVID-19 in a countrywide research conducted in France.

Reduced polymorphonuclear leukocyte mobilization, chemotaxis, and phagocytic activity are further characteristics of hyperglycemia [Price,2010]. A hyperglycemic environment inhibits glucose 6-phosphate dehydrogenase (G6PD), which prevents antibacterial action. It also causes polymorphonuclear leukocytes to undergo more apoptosis and lessens their ability to migrate through the endothelium [Price, 2010]. The proliferative function of CD4 T lymphocytes and their response to antigens through the altered production of cellular adhesion molecules are impacted when glycosylated hemoglobin (HbA1c) is more than 8.0%. (Price,2010)

Two community-based assessments conducted in the UK made it abundantly evident that patients with T1DM had a greater death rate than the population without T1DM. Older age, elevated HbA1c levels, arterial hypertension, renal functional impairment, and a history of cardiovascular events (myocardial infarction, stroke, or heart failure) were risk factors for patients with T1DM (Holman,2020, Barron ,2020). These findings provide credence to the link between T1DM and unfavorable COVID-19 outcomes.

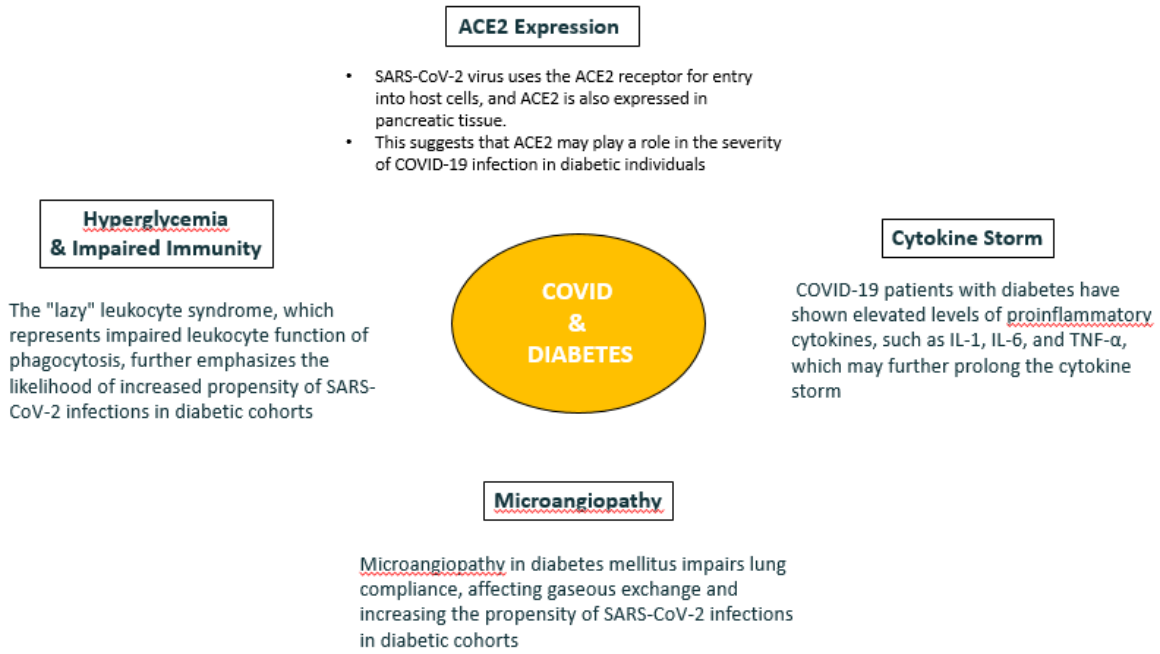

Fig 2: Possible mechanisms of poor COVID- 19 outcomes in Type 2 diabetes mellitus patients (Chidiebere,2020 & Roy,2020)

Management Of Diabetes In COVID-19:

Although not thoroughly investigated, interactions between DPP4 and the RAAS (including ACE2) are plausible (Abouelkheir,2019, Jackson, 2008) . Genetically connected to the severity of COVID-19 and probably the danger of SARS-CoV-2 infection, DPP4 and the RAAS are linked, especially in those with diabetes mellitus (Valencia,2020) . The results showing DPP4 expression was elevated in blood T cells from T2DM patients and was connected with insulin resistance (Lee,2013), as well as the observation that overexpression of DPP4 in diabetic mice

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resulted in immunological response dysregulation, all support this connection. (Romacho,2020). Sitagliptin therapy during hospitalization for COVID-19 was linked to better clinical outcomes and lower mortality in a retrospective case-control study from northern Italy (Solerte,2020) . An additional set of Italian case series reported a statistically significant decrease in mortality associated with DPP4i therapy, however this study had a smaller sample size

GLP-1RAs could effectively treat both non-diabetic and severely affected COVID-19 diabetic patients. Notably, glucose variability—a typical result in COVID-19 patients—is prevented in T2DM patients by utilizing GLP-1RAs. In order to avoid issues caused by glucose fluctuation in T2DM patients with COVID-19, GLP-1RAs such as tirzepatide may be a useful treatment approach. Hyperinflammation is the outcome of highly active inflammatory signaling pathways in COVID-19. In COVID-19 patients, GLP-1RAs lower inflammatory indicators such as ferritin, CRP, and IL-6. Thus, by lowering the inflammatory burden, GLP-1RAs like tirzepatide may be beneficial in COVID-19 patients. Tirzepatide' s anti-obesogenic action may lessen the severity of COVID-19 by reducing body weight and adiposity. Moreover, COVID-19 may cause significant changes in the gut microbiome. Intestinal dysbiosis is avoided and gut microbiota is preserved by GLP-1RA. Here, Tirzepatide, like other GLP-1RA, may lessen the changes in the gut flora brought on by COVID-19. In doing so, it may also help reduce intestinal inflammation and systemic problems in COVID-19 patients who are obese or have type 2 diabetes. According to another study, patients with COVID-19 who have diabetes had a noticeably increased risk of passing away. Additionally, we discovered that metformin therapy lowers mortality and plasma C-reactive protein levels. Maintaining metformin during the hospital stay showed a better prognosis for survival when compared to sulfonylureas. Additionally, it was seen that sulfonylurea use is linked to a higher COVID-19 mortality rate due to a rise in cardiovascular events when compared to metformin. (Rozalia,2023)
Many observational and epidemiological studies have suggested an association between vitamin D insufficiency and the incidence of type 1 and type 2 DM . According to some research, vitamin D therapy may prevent diabetes in people who are pre-diabetic or at high risk of developing it, especially if they have low baseline 25(OH)D levels (Favre, 2021). Low 25(OH)D levels may be a risk factor for the two-way relationship between diabetes and COVID-19, making diabetics more vulnerable to the virus on the one hand and encouraging COVID-19's diabetogenic effect on endothelial dysfunction and microvascular complications on the other. An adjuvant treatment for COVID-19 individuals with diabetes and a vitamin D status deficiency, our umbrella review showed that vitamin D supplementation improves circulating inflammatory biomarkers in subjects with diabetes. Therefore, it can be confirmed that, based on this comprehensive study, there is a compelling argument for the therapeutic administration of extra vitamin D to lessen COVID-19 respiratory problems or, in the event of an infection, to stop the development of a serious COVID-19 infection. The solution to the clinical heterogeneity issue is the analysis's main point of strength. (Argano, 2022). When SGLT2I is used in critically sick patients, it may be a challenge because these patients require close monitoring of their fluid balance and risk of developing diabetic ketoacidosis (Hahn,2018) . Nonetheless, for patients with COVID-19, DARE-19 is the only sizable randomized controlled trial that will examine the safety profile of dapagliflozin in this patient population as well as if

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it can prevent COVID-19-related complications and all-cause mortality in addition to enhancing clinical recovery. (Kosibarod, 2021)

Focus areas on future research:

- To better contextualize the risk of diabetes following SARS-CoV-2 within the larger post-viral situation, long-term comparative investigations of the risks of diabetes following SARS-CoV-2 vs other viral illnesses (such as seasonal influenza) are needed.
- Studies examining whether antivirals or other therapeutics during the acute or post-acute phase of COVID-19 reduce the risk of diabetes (or other post-acute sequelae)
- Longitudinal research aimed at understanding the health trajectories and outcomes of individuals with diabetes after the virus, including response to treatment, utilization of health resources, and downstream health outcomes.
- Longer-term research to ascertain whether diabetes and other cardio-metabolic consequences in COVID-19 patients become chronic conditions over time or if they resolve with time.
- Research assessing the impact of novel vaccinations and boosters, SARS-CoV-2 variations and sub-variants, and the recurrence of infections on the epidemiology of post-acute sequelae, such as diabetes.

Limitations and Future Directions

While the reviewed studies provide compelling evidence for a potential association between COVID-19 and NODM, some limitations remain. Many studies are observational, making it difficult to establish a definitive causal relationship. Additionally, the long-term impact of COVID-19 on diabetes risk requires further investigation. Future research should focus on randomized controlled trials to determine the efficacy of preventative measures and treatment strategies for NODM in the context of COVID-19. Exploring the role of genetics and individual susceptibility to NODM post COVID-19 infection would also be valuable.

Conclusion:

The growing body of evidence suggests a concerning link between COVID-19 and the development of new-onset diabetes. Studies have shown an increased risk of new-onset diabetes after recovering from COVID-19 compared to non-COVID-19 individuals. The risk of diabetes post-COVID-19 infection appears to be elevated across different age groups, genders, and severity levels of COVID-19, emphasizing the importance of monitoring glucose metabolism in the post-acute phase of the disease. Furthermore, the association between COVID-19 infection and incident diabetes seems to be graded by the severity of the initial COVID-19 infection, with higher risks observed in younger patients and those with more severe disease. These findings underscore the need for healthcare providers to be vigilant about monitoring and managing diabetes in individuals who have recovered from COVID-19. Understanding the increased risk of diabetes post-COVID-19 infection is crucial for public health strategies, emphasizing the importance of preventive measures, including vaccination and chronic disease management, to mitigate the long-term health impacts associated with COVID-19.

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