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**Review**

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# Long COVID-19 and diabetes mellitus: a short review

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## Abstract

The persistence of Covid-19 infection for more than four weeks after the acute phase is defined as the long Covid-19 syndrome. This condition, otherwise defined by the persistence of signs and symptoms for more than 12 weeks, shares several features with diabetes mellitus: diabetes mellitus and Covid-19 infections have a pandemic dimension, are characterized by an inflammatory milieu, and show a bidirectional relationship. Diabetic patients appear more likely to develop long Covid-19 syndrome than non-diabetic individuals. The chronicity of Covid-19 favors the development of new cases of diabetes. In this short review, we discuss the evidence supporting the link between Covid-19 and diabetes mellitus, focusing on the epidemiological and pathophysiological aspects of this dangerous relationship.

### Highlights

- Patients affected by diabetes both type 1 and type 2 seem more likely to develop a long Covid-19 syndrome compared to non-diabetic subjects;

- Long Covid-19 syndrome is associated with new-onset cases of diabetes, both type 1 and type 2 higher than expected;

- Presence of other comorbidities prior to acute Covid-19 infection favors the development of long Covid-19 syndrome;

● Most frequent symptoms of long Covid-19 in diabetic patients are fatigue, shortness of breath, neurocognitive and neurological manifestations, and cardiovascular sequelae;

● Long Covid-19 can exacerbate microvascular dysfunction in patients with diabetes.

**Keywords:** Post-COVID, diabetes mellitus, long Covid-19 pathophysiological mechanisms

## INTRODUCTION

Diabetes mellitus is a chronic disease with a worldwide prevalence of 9.3%; this figure is expected to increase to 10.2% (578 million) by 2030[1], representing a condition of such epidemiological relevance that it can be considered a pandemic. Similarly, Coronavirus disease 2019 (Covid-19) was considered a pandemic, with 756,581,850 cumulative cases and 6,844,267 cumulative deaths worldwide from its spread in 2019, until now (February 14th, 2023) (https://covid19.who.int/). Covid-19 is caused by an RNA virus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), whose presentation ranges from asymptomatic infection to a multi-system disease[2,3]. The respiratory system is the primary target of the virus; however, many other organs can be deranged by this disease, resulting in severe clinical manifestations such as acute coronary syndromes, myocardial dysfunction and arrhythmias, acute kidney injury, gastrointestinal and hepatocellular injury, metabolic disturbances (hyperglycemia, ketosis), neurologic illnesses, muscular diseases, dermatologic manifestations, and thrombotic complications[4]. A robust association between diabetes and Covid-19 emerged early during the pandemic; SARS-CoV-2 infection and diabetes share two fundamental features: the inflammatory state and the multiorgan involvement and damage[5]. The pathophysiological mechanisms underlying the link between Covid-19 and diabetes have not been fully elucidated; indeed, Covid-19 infection can alter glucose metabolism, making glycemic control particularly challenging in patients with diabetes[6]. Often, recovery does not occur, and many symptoms and disturbances persist over time, generating long Covid-19 (or post-Covid-19) syndrome. The prevalence of long Covid-19 has been reported between 10% and 30% of individuals affected by acute Covid-19[7,8].

The presence of diabetes (type 1 or 2) in subjects with acute SARS-CoV-2 infections appears to worsen all outcomes, including mortality[9-16]. Diabetes mellitus represents the second leading comorbidity in patients who have died from Covid-19 infection[17], after hypertension[18]. The risk of dying in a hospital with Covid-19 appears to have at least doubled in individuals with diabetes[19]. In a study conducted in England, Barron *et al*. reported an odds ratio for in-hospital Covid-19-related mortality of 3.51 (95%CI: 3.16-3.90) in people with type 1 diabetes and 2.03 (95%CI: 1.97-2.09) in people with type 2 diabetes[12]. These effects were attenuated but remained significant after adjustment for previous coronary heart disease, cerebrovascular disease, or heart failure requiring hospitalization[12]. Covid-19 outcomes depend on comorbidities, particularly obesity and cardiovascular disease, primarily relevant in diabetic patients. Obesity (particularly visceral obesity) with a dysmetabolic condition characterized by subclinical inflammation can determine Covid-19 severity and is a significant risk factor for its development[20]. Many studies investigated the relationship between acute Covid-19 and diabetes; however, few studies addressed the association between diabetes and long Covid-19 [Table 1]. Given the clinical and socioeconomic burden of these major diseases, long Covid-19 syndrome in subjects with diabetes deserves a careful evaluation.

In this short review, the epidemiological and pathophysiological aspects of the relationship between long Covid-19 and diabetes will be discussed.

**Table 1. Studies investigating the relationship between diabetes, either type 1 or 2, and long Covid-19 disease**

| Authors [Reference] | Article type | Diabetes type considered | Conclusions |
|---|---|---|---|
| Feldman *et al.*[5] | Review | Types 1 and 2 | Diabetes may be at risk for long Covid-19 (to be determined) |
| Sudre *et al.*[7] | Observational | Not specified | Diabetes is a risk for long Covid-19 |
| Greenhalgh *et al.*[29] | Practical management | Not specified | Many patients with long Covid-19have diabetes |
| Mittal *et al.*[30] | Prospective case-control | Type 2 | T2D patients are more symptomatic than controls |
| CDC[37] | Practical management | Not specified | People who have had COVID-19 may be more likely to develop diabetes |
| Shin *et al.*[38] | Experimental study | Type 2 | Diabetes and visceral adiposity are major risk factors for the severe progression of COVID-19 |
| Liang *et al.*[40] | Observational prospective | Not specified | Diabetes mellitus was one of the most common pre-existing illnesses in long Covid |
| Huang *et al.*[41] | Cohort | Not specified | Diabetes is the second most common comorbidity in long Covid-19patients; Some participants were newly diagnosed with diabetes |
| Al-Aly *et al.*[54] | Cohort | Type 2 | Increased incident diabetes during post-Covid-19 |
| Xie *et al.*[55] | Cohort | Types 1 and 2 | Increased incident diabetes during post-Covid-19 |
| Barrett *et al.*[58] | Retrospective cohort | Types 1 and 2 | Increased incident diabetes during post-Covid-19 |
| Ayoubkhani *et al.*[60] | Retrospective cohort | Types 1 and 2 | Increased incident diabetes during post-Covid-19 |
| Estiri *et al.*[40] | Observational retrospective | Type 2 | T2D is a risk for long Covid |
| Steenblock *et al.*[50] | Review | Types 1 and 2 | T2D is a risk for long Covid<br>T1D is increased after Covid-19 favors T1D |
| Thompson *et al.*[51] | Longitudinal studies | Not specified | No increased risk of long Covid-19in diabetes |
| Tazare *et al.*[59] | Cohort study | Type 2 | Post-Covid-19 higher risk of T2D |
| Vlad *et al.*[73] | Observational | Type 1 | Newly diagnosed T1D uring Covid-19 significantly higher at one year |
| Tittel *et al.*[74] | | Type 1 | No short-term influence of the Covid-19 |

## LONG COVID

Long Covid-19 is characterized by symptoms persisting after a previous acute SARS-Cov-2 infection. Covid-19 can be defined depending on its duration, as specified by NICE guidelines[21]. Acute Covid-19 disease is defined as signs and symptoms lasting for up to 4 weeks; ongoing Covid-19 disease occurs when signs and symptoms are present from 4 weeks up to 12 weeks; post-Covid-19 syndrome is as the persistence of signs and symptoms for more than 12 weeks, and an alternative diagnosis does not explain these; finally, the long Covid-19 includes ongoing symptomatic Covid19 and the post-Covid19 syndrome (12 weeks or more)[21].

The World Health Organization defined clinical cases of long Covid-19 as "occur(ing) in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of Covid-19 with symptoms and that last for at least two months and cannot be explained by an alternative diagnosis"[22].

Therefore, long Covid-19 refers to persisting debilitating symptoms, with multiorgan origin and different intensity, persisting 1-3 months after an acute infection from the SARS-CoV-2 virus, without an alternative explanation.

The prevalence of symptoms after three months after Covid-19 ranges from 3%-11.7% of affected subjects in an analysis performed in the UK[23]; a study in the United States reported a prevalence of post-Covid-19 at

8.3%-13.8% of SARS-CoV-2 infections; this figure corresponds to 1.2%-1.9% of the American adult population, with a prevalence higher in females than males and highest in the 50-64 year group[24].

Clinical presentation of long Covid-19 can be characterized by persisting symptoms after the resolution of the acute phase or even by new-onset symptoms[25]. The most common long-term symptoms are persistent dyspnea and shortness of breath; chronic fatigue; general neurological decay and cognitive dysfunction; smell and taste disturbances; body aches; symptoms referrable to the central and peripheral nervous system, musculoskeletal system and immune system; sleep difficulties; anxiety and depression; and other various disturbances. This multi-system disease presentation generally harms everyday life to varying degrees; however, it is seldom accompanied by severe limitations[26-28]. Moreover, long Covid-19 syndrome can be characterized by a cluster of symptoms (which can affect any organ), and these symptoms can change over time, either in intensity or presentation; they are not necessarily associated with the organ dysfunctions manifested during the acute phase of the disease[7,29].

Type 2 diabetic subjects with a long Covid-19 syndrome often complain of fatigue[30]. Already sarcopenic older type 2 diabetic females have relatively steeper declines in functional capacity (e.g., excessive fatigue and difficulty walking) and delayed recovery from Covid-19 than other groups[30,31]. Moreover, SARS-CoV-2 infection can favor the rapid onset of sarcopenia due to concomitant causes such as long hospitalization, nutrient deficiency, and steroid therapy[32]. A high proportion of diabetic patients (up to 88%) reported at least one long-term persistent symptom[33]. Neurocognitive dysfunction, neurological manifestations, shortness of breath, and cardiovascular sequelae are often reported by diabetic subjects[5,34,35]. Furthermore, Covid-19 can exacerbate microvascular dysfunction in patients with diabetes[36]. Against this background, two questions could be asked: (1) Does diabetes increase the risk of developing a long Covid-19 syndrome, and conversely, (2) Does long Covid-19 syndrome increase the risk of diabetes?

## DIABETES MELLITUS AS A RISK FACTOR FOR LONG COVID

Diabetes mellitus does not appear to be a risk factor for acute Covid-19 infection but can worsen its outcomes. On the other hand, it appears to be a risk factor for developing long Covid-19 syndrome. People in poor health before acute Covid-19 are more likely to develop long Covid-19[37]. Poor metabolic health (e.g., in type 2 diabetic and obese subjects) increased the risk of SARS-CoV-2 infection and complicated Covid-19 through hyperglycemia, hyperinsulinemia, and insulin resistance[38] [Figure 1]. These conditions might drive immunosenescence and make vaccination less effective in these subjects[39]. Comorbidities are present in around one-third of subjects developing long Covid-19 syndrome[40]. Diabetes, hypertension, cardiovascular disease, pulmonary disease, and obesity are the most common comorbidities in patients who develop long Covid-19 syndrome[41,42]. A significantly higher risk of incident diabetes (most likely new-onset type 2 diabetes) was observed in a pooled analysis of 5,787,027 post-acute Covid-19 subjects[43].

Relatively few studies addressed the question if diabetes is a risk factor for the long Covid-19 syndrome, and many of these have small sample sizes and short follow-up periods; nevertheless, diabetes appears to be associated with persistent fatigue, dyspnea on exertion and musculoskeletal pain[5,44-47]; the literature does not draw consistent conclusions. Estiri *et al*. found that type 2 diabetes was a risk factor for long Covid-19 among non-hospitalized Covid-19 patients; in their study of 9025 subjects with positive test results, there were 33 phenotypes indicative of long Covid-19[48]. Of these, diabetes showed an OR of 1.41 (95% CI: 1.22-1.64)[48]. In another prospective observational cohort study, diabetes appeared to be a more significant predictor of long Covid-19 (> 56 days; diabetes 5.8 %) than short Covid-19 (< 10 days; diabetes 3 %)[7]. Long Covid-19 incidence was exceptionally high in those with comorbid disease. Diabetes mellitus is (with arterial hypertension) the most common comorbid disease in patients who

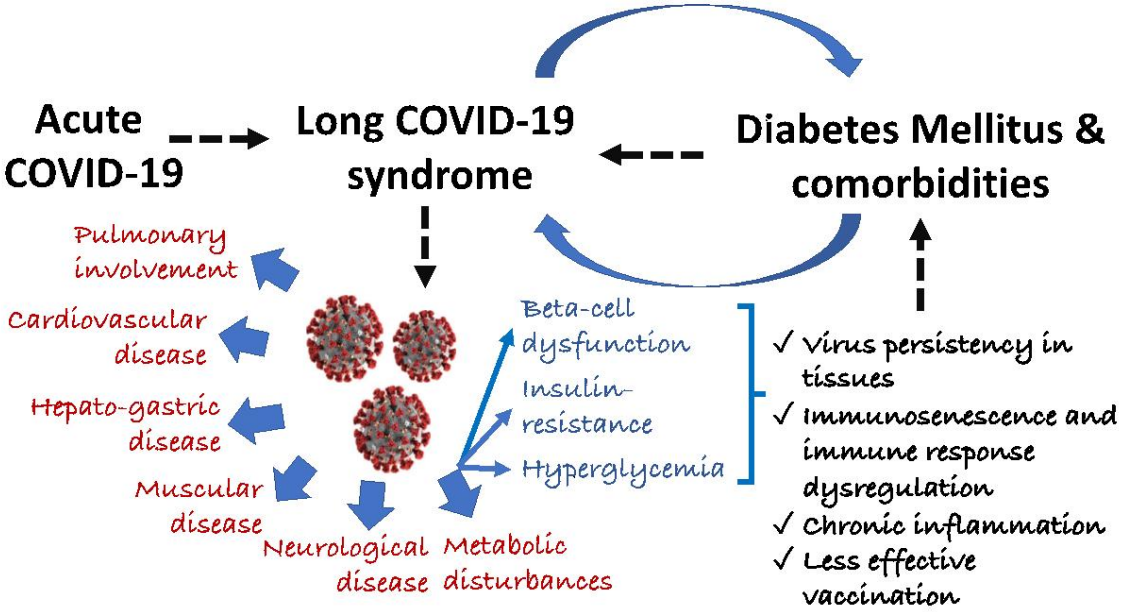


**Figure 1.** Diabetes mellitus appears to have a bidirectional association with the long Covid-19 syndrome: the persistence of SARS-CoV-2 infection can damage pancreatic beta-cells and induce an insulin resistance state. On the other hand, the presence of diabetes mellitus appears to favor the long Covid-19 syndrome.

develop long Covid-19 syndrome after hospitalization[49]. Other authors suggested that Covid-19 survivors affected by diabetes could have a higher risk for long-term sequelae[5,36,50].

However, although most studies found that diabetes represents a risk for long Covid-19, not all confirmed this observation. Indeed, Fernandez-de-las-Penas *et al.* found no association between diabetes and post-Covid-19 symptoms. This case-control study included patients with diabetes and 144 control subjects with Covid-19 infection. Patients were followed up for a mean of 7.2 months[45]. In that study, long Covid-19 developed independently of diabetes. The lack of robust evidence of associations for long Covid-19 outcomes with diabetes or other comorbid conditions such as arterial hypertension or high cholesterol was suggested by a recent study; data were collected from ten longitudinal studies and electronic health records in the UK[51]. There was a U-shaped association of long Covid-19 risk with age, with the highest risk in individuals aged 45-54 and 55-69 years[51].

Unfortunately, these studies often do not discriminate between diabetes types; therefore, we cannot conclude types 1 or 2 diabetes, although the substantial imbalance between the prevalences implies that most patients had type 2 diabetes; few studies included type 1 diabetic patients. The multicenter French Coronavirus SARS-CoV-2 and Diabetes Outcomes (Coronado) study[52] found similar Covid-19 outcomes in type 1 and 2 diabetes patients; however, there were only 39 type 1 subjects.

Prediabetes has also been considered a predisposing factor for long Covid-19 syndrome. However, although prediabetes increased the risk of developing severe Covid-19, it did not appear to be significantly associated with long Covid-19[53]. To summarize, evidence suggests that diabetic subjects are more at risk of long Covid-19 syndrome than non-diabetic individuals; however, more studies are needed to draw definitive conclusions.

## LONG COVID-19 AS A RISK FACTOR FOR DIABETES MELLITUS

There is robust evidence suggesting that coronavirus is associated with a new diagnosis of diabetes, particularly in specific subgroups[23,54-60]. Some authors reported an increase in new-onset diabetes (types 1 and 2) in the acute and post-acute Covid-19 disease, supporting a robust bidirectional relationship between SARS-CoV-2 infection and diabetes[46,47,61-69]. In a meta-analysis of eight studies with more than 3,700 patients, Sathish et al. demonstrated a pooled proportion of 14.4% for newly diagnosed diabetes in hospitalized patients for Covid-19[56].

An increased burden of metabolic disturbances and diabetes was found in the United States Department of Veterans Affairs database among 6-month incident sequelae in patients who survived for at least 30 days after Covid-19[54]. Xie *et al.* studied the same cohort and compared 181,280 patients with Covid-19 to a control group enrolled during the same period (but without Covid-19 and with a historical control group from the pre-pandemic era). The authors reported a significantly increased risk of incident diabetes and anti-hyperglycemic drug use in subjects previously affected by Covid-19 at the 12-month follow-up[55]. In this study, diabetes was associated with the severity of Covid-19 infection, advanced age, cardiovascular risk, obesity, prediabetes, and Black race. Montori contributed a commentary to the article[70], stating that incident diabetes occurred in one of every 100 people affected by Covid-19 at one year; the incidence was two more per 100 if they were prediabetic before Covid-19.

A descriptive study of survivors of severe Covid-19 in England that used data from the OpenSAFELY platform linked primary care records to death certificates and hospital data; the authors demonstrated that the rate of type 2 diabetes was high during the four months after hospital discharge and this was especially evident during the first month (adjusted-hazard ratio 1.28; 95%CI: 1.08-1.50)[59].

In a prospective longitudinal study conducted in Wuhan and including 248 discharged patients, Zhang *et al.* found that severe Covid-19 was associated with an increased risk of diabetes incidence at 1-year follow-up, with an OR = 2.90, 95%CI: 1.07, 7.88)[57]. Male patients appeared to be more vulnerable. In the same study, having diabetes and hypertension increased the risk of persistent symptoms, mainly tiredness and fatigue, palpitations, chest tightness, shortness of breath, cough, and productive cough.

Ayoubkhani *et al.* compared the manifestations of post-Covid-19 syndrome to matched controls in a comprehensive retrospective study of 47780 patients admitted to the hospital for acute Covid-19 in England[60]. People discharged from the hospital after acute infection was diagnosed with diabetes (types 1 or 2) 1.5 (1.4-1.6) times more frequently than the matched control group during a mean follow-up of 140 days[60]. The authors concluded that individuals discharged from the hospital after Covid-19 showed higher rates of multiorgan dysfunction than the general population, and this result was independent of age[60].

It has been suggested that cardiometabolic syndrome per se, i.e., a group of interacting clinical abnormalities that often develop into diabetes, cardiovascular diseases, and chronic renal failure, could represent frequent sequelae of long Covid-19 and a significant future burden for health systems[71].

Increased incidence of pediatric type 1 diabetes has also been reported during the acute phase of Covid-19[72,73], and increased new diagnoses of type 1 diabetes were reported in the post-acute phase. A study from the United States investigated the incidence of diabetes in people aged < 18 years at > 30 days after an acute SARS-CoV-2 infection[58]. In that study, diabetes diagnoses were culled from retrospective cohorts in the IQVIA and the Health Verity databases. Patients were compared with subjects matched by age and sex who were not diagnosed with Covid-19 during the pandemic or had had a non-Covid-19 acute respiratory

infection before the pandemic. Unfortunately, the type of diabetes was not ascertained in this study, which found a hazard ratio for diabetes of 2.66 (95%CI: 1.98-3.56) in subjects in the Covid-19 group versus subjects in the non-Covid-19 group[58]. On the other hand, respiratory infections not due to SARS-CoV-2 were not associated with an increased risk for diabetes[58].

Two German observational studies investigated the incidence of type 1 diabetes concerning Covid-19 at different periods. In 2020[74], the authors reported a lack of a short-term influence of the Covid-19 pandemic on diabetes incidence. In 2022, the same authors described a long-term increase in type 1 diabetes, with an incidence significantly higher than expected in children and adolescents after the Covid-19 epidemic; the peak incidence of diabetes followed the peak incidence of SARS-CoV-2 infection by three months[75]. It is challenging to explain this association's causes and timing, and they are probably multiple and unclear. The authors suggested that the cytotoxic and immunologic direct effects on pancreatic beta-cells caused this increase after the pandemic; they also suggested that diabetes onset could be the indirect result of environmental changes caused by the pandemic or the containment measures[75].

An abnormal metabolic milieu (i.e., obesity, insulin resistance, diabetes mellitus, and prediabetes) represents an unfavorable condition and a risk factor for severe acute presentation of Covid-19 disease and sequelae of post-acute Covid-19 syndrome[76]. Nevertheless, the pathophysiological interplay between these conditions is not yet wholly understood.

## POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS OF POST-COVID-19 DIABETES

Acute SARS-CoV-2 disease can worsen glucose metabolism in diabetic patients[77]; however, the persistence of the infection can be associated with new cases of diabetes mellitus. The possible pathophysiological mechanisms contributing to disturbances involving many organs during long Covid-19 are summarized in a review by Castanares-Zapatero *et al.*[78]. The authors describe multiple and intertwined mechanisms to determine long Covid-19. Among these are virus-driven cellular alterations related to the neurotropism of this virus, dysregulation of the immune response, and persistent and occult presence of the virus in different organism tissues. These disturbances could play a relevant role in the chronicity of the disease[78]. Long Covid-19 might be attributable to the persistence of residual Covid-19 infection in various internal organs. To support this hypothesis, intestinal biopsies from subjects previously afflicted with acute SARS-CoV-2 infection showed the persistence of the infection in the gastrointestinal tract[79,80]. The persistence of the infection was also demonstrated in islets of Langerhans[81]; these findings could explain one of the many etiopathogenetic mechanisms of Covid-19 related to diabetes.

It has been suggested that Covid-19 can precipitate new-onset diabetes mellitus weeks to months after the resolution of the acute infection, again through beta cell direct infection and a derangement of the immunity system[82]. Several mechanisms might participate in determining diabetes after an acute SARS-CoV-2 infection; however, a relationship between Covid-19 and the risk of developing diabetes has not been elucidated. Potential pathogenic metabolic mechanisms that could underly severe acute Covid-19 and post-acute disease sequelae are multifactorial because of the multifaceted disease presentation and the extent of the tissue injury[76,83].

The inflammatory state induced by Covid-19 is very similar to that observed in type 2 diabetes; however, it is often amplified[84-86]. Diabetes is characterized by chronic subclinical inflammation, featuring increased circulating levels of TNFα, IL-6, and IL-1β that induce and maintain the insulin resistance state. In acute SARS-CoV-2, a sudden and massive overproduction of pro-inflammatory cytokines ("cytokine storm") can lead to multiorgan failure that is often severe, diffuse, or fatal[86]. In Chinese studies, patients with diabetes

showed a more inflammatory profile than their non-diabetic counterparts[11,87]. The pathophysiology of type 2 diabetes following Covid-19 infection is characterized by an inflammatory milieu enhanced by Covid-19 infection that damages beta cells, accelerating their exhaustion and contributing to insulin resistance[88-90].

Experimental and autopsy studies demonstrated that specific mechanisms could drive beta cell damage and apoptosis, leading to type 1 diabetes[81,91,92]. SARS-CoV-2 can induce beta cell death by direct infection[91]. SARS-CoV-2 damages beta cells, allowing viral entry via various receptors. To gain entry, the virus binds to angiotensin-converting enzyme 2 receptors and other proteins expressed on beta cells. Therefore, pancreas islets could represent a target for the cytotoxic effects of Covid-19, triggering the development of types and type 2 diabetes mellitus[93].

It has been suggested that SARS-CoV-2 could lead to ketosis-prone diabetes via binding to ACE-2 receptors and directly destroying the cells[62]. These receptors are abundant in pancreatic beta cells and adipose tissue; through this mechanism, Covid-19 infection determines beta cell destruction and consequent glucose metabolism abnormalities[94,95]. Almost ten years before the Covid-19 pandemic, SARS-CoV was demonstrated to induce beta cell damage and insulin-dependent diabetes through ACE-2 receptor binding[96]. The transmembrane serine protease protein is needed to enter SARS-CoV-2 in human beta-cells[97]; once entered, the virus infects and replicates, resulting in impaired production and secretion of insulin[56]. Beta cells also express high levels of neuropilin-1 receptor critical for viral entry, causing cell death and reduced insulin secretion[91,98]. Through these mechanisms, SARS-CoV-2 infection attenuates pancreatic insulin levels and secretion.

However, in vitro studies suggest that direct infection of pancreatic cells is unlikely to explain new-onset diabetes in individuals with long Covid-19 fully. The primary deficit in insulin production is probably mediated by inflammation or the infection stress response with peripheral insulin resistance[99]. Insulin resistance is a significant pathogenetic mechanism leading to overt diabetes; insulin resistance could be ascribed to persistent low-grade inflammation[83,100]. Other potential mechanisms could be considered with these abnormalities of the immunological profile. The immunological response in patients with long Covid-19 differs from those who recover; the virus-induced autonomic dysfunction could contribute to insulin resistance[83,101,102]. Furthermore, some authors suggest that the increased incidence of type 1 diabetes in children during the pandemic should not be due to SARS-CoV-2 infection but could be mediated by pathogens such as enteroviruses or changes in environmental factors (i.e., sunlight exposure and vitamin D levels)[103]. Some authors could not identify a higher incidence of type 1 diabetes during the pandemic than before[104,105]. There is no evidence that diabetes manifesting in long Covid-19 can be reversed after the acute phase.

Finally, long Covid-19 could also play a causal role in the development or progression of microvascular complications of diabetes because SARS-CoV-2 affects microcirculation, causes endothelial cell swelling and damage, micro-thrombosis, disrupts capillary integrity and barrier function, and impairs tissue repair[106].

## IMPACT OF VACCINATION ON LONG COVID-1919 DEVELOPMENT IN DIABETIC SUBJECTS

Vaccination against Covid-19 has been highly effective in combating the SARS-CoV-2 pandemic[107], reducing acute symptoms, hospitalization, and death; however, patients with diabetes (especially those with uncontrolled glycemia) appear to be less responsive to the protective effects of the vaccination[39,108]. Moreover, vaccines are sometimes seen as potentially harmful. In a recent survey, subjects unvaccinated prior to infection showed a higher risk of reporting 28 or more days of Covid-19 symptoms, and these

patients were more likely to be diabetic[109]. Whether the vaccination can protect diabetic subjects from developing a long Covid-19 syndrome is unclear. Studies are needed to determine the impact of vaccines in reducing the long Covid-19 syndrome and new-onset diabetes[110].

## FUTURE PERSPECTIVES ON DIABETES AND LONG COVID-19

The long Covid-19 syndrome is far from completely understood, particularly in populations with diabetes. We need more robust data to conclude the relationship between diabetes and long Covid-19, including the role of vaccination. Many questions remain to be addressed.

- The mechanisms underlying long Covid-19-associated new-onset diabetes;
- The impact of long Covid-19 on the management of pre-existing diabetes;
- The relationship between anti-diabetic drugs and long Covid-19 syndrome;
- The impact of vaccination in preventing long Covid-19 syndrome in diabetes.

And many others. We hope that ongoing and future studies can give further insights to better frame the long Covid-19 syndrome in diabetes mellitus.

## CONCLUSIONS

Although vaccination appears to have reduced the risk of a long Covid-19 syndrome[111], this condition can develop in a significant number of individuals who suffered acute Covid-19 disease, with substantial deleterious impact on affected individual health, their social and professional life, sometimes substantially deteriorating the daily activities and the general wellbeing. Diabetes mellitus appears to have a bidirectional association with the long Covid-19 syndrome [Figure 1], being a cause and a consequence of the chronicity of SARS-CoV-2 infection. In diabetic patients, the diagnosis, treatment, and prevention of post-Covid-19 syndrome are becoming urgent health needs. Research is required to focus on this new issue.

## DECLARATIONS

### Authors' contributions

Conceived and wrote the article: Vigili de Kreutzenberg S

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### Conflicts of interest

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### Ethics approval and consent to participate

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### Consent for publication

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