Research Article

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Increased Risk of New-Onset Diabetes after Recovery from COVID-19

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ABSTRACT

Background: *Several studies reported increased incidence of diabetes in individuals who recovered from coronavirus disease 2019 (COVID-19) caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2).*

Objective*: To determine risk, characteristics and potential mechanisms of new-onset diabetes in patients who recovered from COVID-19.*

Methods: *PubMed search up to May 26, 2022. Search terms are diabetes, hyperglycemia, SARS-CoV-2, COVID-19, cytokines, glucocorticoids. Cohort retrospective studies, pertinent in-vitro studies, pre-print and review articles are included.*

Results: *Large retrospective cohort studies have consistently shown increased risk of diabetes, mainly type 2, during a follow-up period of approximately 6-18 months after recovery from acute COVID-19. One cohort study also showed increased risk of diabetes (94% of cases were type 1 and type 2 diabetes) among pediatric population in the post COVID-19 period. Increased risk of incident diabetes occurred in non-hospitalized and hospitalized patients with COVID-19, with gradual incremental risk occurring in parallel to the severity of COVID-19. The largest cohort study has shown that older age, black race, higher body mass index (BMI), presence of cardiovascular disease, hypertension, and pre-diabetes further increased incident type 2 diabetes after COVID-19. Risk of new-onset diabetes after COVID-19 infection was greater than those following respiratory infections unrelated to COVID-19. Mechanisms of development of diabetes in the post-COVID-19 duration are unclear and likely multifactorial. Persistence of altered cytokines after apparent clinical cure of COVID-19 might worsen insulin resistance. In addition, direct invasion of pancreatic β-cells by SARS-CoV-2 could be among the underlying mechanisms.*

Conclusions: *New-onset type 2 diabetes may be one of the sequelae of COVID-19 infection. Physicians and patients should be aware about the possible occurrence of this complication for early diagnosis and treatment.*

Keywords

Diabetes, COVID-19, Cohort, Glycemic control, Cytokines, Pancreatic β-cells.

Introduction

COVID-19 has been shown to worsen glycemic control, trigger hyperglycemic crisis, and induce new-onset diabetes [1,2]. More recently, growing body of evidence suggest in addition that COVID-19 confers increased risk of development of diabetes after clinical recovery from the disease in the post-COVID-19 period. The main purpose of this article is to review available data regarding risk, characteristics and potential mechanisms of new-onset diabetes following recovery from COVID-19.

Studies That Examined Incident Diabetes among Other Post-COVID-19 Disorders

Several retrospective studies examined incident diabetes among other conditions that emerged after the acute phase of

SARS-CoV-2 infection. Daugherty et al. [3] used US national administrative data base of 266,586 COVID-19 patients (8% required hospital admission) to compare incidence of diabetes and other disorders such as chronic respiratory failure, cardiac arrythmia, hypercoagulability, peripheral neuropathy and amnesia with a control group matched by propensity scoring. The hazard ratios (HR) of most these conditions were increased in the 6 months following acute COVID-19. Regarding diabetes risk, there was significant increase in incident diabetes in the post-COVID-19 group versus control group, HR being 2.47 (95% CI, 1.14-5.38) [3]. In a retrospective study from the UK, including much sicker patients (n=47,780, mean age 65 years, 55% women) who all required admissions for COVID-19, Ayoubkhani et al. [4] compared the incidence of diabetes, respiratory and cardiovascular diseases with a matched control group of individuals from the general population over mean follow-up of 140 days. During this follow-up, 12.3% of patients died and 29.4% were re-admitted to the hospital [4]. The rate ratio of incident diabetes in the post-COVID-19 group was 1.5 (95% CI, 1.4-1.6) compared with matched control subjects. The risk of incident diabetes was higher in those younger than 70 years and in non-white individuals (28% of patients) [4].

In a retrospective investigation (non-peer-reviewed) from the UK using national electronic health records obtained from a database called "Open SAFELY" platform, the authors selected 3 cohorts: all patients hospitalized with COVID-19 in 2020, a comparison matched group including all patients hospitalized with non-COVID-19 pneumonia in 2019, and a third control group from the general population [5]. Besides incident type 2 diabetes, the authors measured the frequency of the following 7 outcomes over 9 months of follow-up: deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction, heart failure and acute renal injury [5]. When compared with general population, the frequency of all outcomes was increased among post-COVID-19 patients. HR of incident type 2 diabetes was 3.96 (95% CI, 3.46-4.53) [5]. Interestingly, when compared with the non-COVID-19 pneumonia group, risk of type 2 diabetes remained significantly greater in the COVID-19 group, HR 1.23 (95% 1.05-1.44) [5]. Conversely, risk of all other outcomes was slightly lower in the post-COVID-19 group than in the non-COVID-19 group.

Retrospective Studies That Examined Incident Diabetes as the Only Outcome in the Post-COVID-19 Period

Studies that focused on diabetes incidence as the only outcome after COVID-19 may provide better data quality than those with multiple outcomes. This is because matching and control for multiple covariates pertinent to diabetes (e.g. family history of diabetes, ethnicity, baseline hemoglobin A1c values) are more feasible than in studies with multiple outcomes. Table 1 summarized design and main results of these studies. The best designed retrospective study available is conducted by Xie and Al-Aly [6]. These 2 investigators examined the incidence of diabetes in US veterans affairs (VA) patients (n=181,280, 88% males) who recovered from COVID-19 during the period from 30 days after diagnosis of COVID-19 (i.e. after the acute phase of the disease) to a median follow-up of 352 days (interquartile range 245-406 days). For comparison, they used 2 non-COVID-19 control groups, a contemporary group who used the VA services in 2019 and a historical group who used the VA services in 2017 [6]. These authors found significant increase in risk of development of type 2 diabetes (more than 99% of incident diabetes was type 2) in patients with prior COVID-19 compared with contemporary control subjects, HR 1.40 (95% CI, 1.36-1.44). In addition, patients with previous COVID-19 exhibited increased risk of new antihyperglycemic use, HR 1.85 (95% CI, 1.78-1.92). Similar results were demonstrated when using the historical group as control subjects. Importantly, the risk of incident diabetes increased in parallel to the clinical severity of COVID-19. Thus, HRs for incident diabetes were 1.25 (95% CI 1.21-1.29), 2.73 (95% CI, 2.5-2.99), and 3.76 (95% CI, 3.24-4.37) among patients who were non-hospitalized, hospitalized and those admitted to intensive care, respectively [6]. In addition, subgroup analysis showed that COVID-19 was associated with an increased risk of diabetes across age (≤65 years and > 65 years), gender (males and females), and categories of BMI, socioeconomic conditions, and baseline diabetes risk scoring [6]. Meanwhile, frequency of newly diagnosed diabetes was relatively higher among people older than 65 years than younger patients, Whites (vs Blacks), among those with greater BMI, those with cardiovascular disease, hypertension, dyslipidemia and pre-diabetes compared with subjects without these conditions [6].

In another retrospective VA study conducted at a different time period, Wander et al. [7] examined incident diabetes in a cohort of US veterans after COVID-19 (n=126,710) compared with a matched control group of Veterans who did not have COVID-19. After a mean duration of 193 days post-COVID-19, the risk of diabetes (type not specified) was significantly increased in men only, odds ratio being 1.95 (95% CI, 1.80-2.12), but not in women [7]. Indeed, this is the only study that showed gender difference in incident diabetes after COVID-19. This finding could be partly related to the smaller number of women who represented 16% of the cohort [7]. Nevertheless, the results of the study of Xie and Al-Aly [6] may be more valid than those of Wander et al. [7] due to its larger size, longer duration of follow-up and performance of 9 sensitivity analyses to verify the robustness of their data. For instance, Xie and Al-Aly [6] adjusted for steroid use during the acute phase of COVID-19, and the HR (95% CI) of incident diabetes was almost identical 1.39 (95% CI, 1.36-1.44) after such adjustment implying that steroid administration plays a minor role, if any, in post-COVID-19 diabetes.

Birabaharan et al. [8] extracted data from a federated health research network in the US to evaluate new-onset diabetes over 6 months after mild (n=313,924) and moderate/severe (n=10,436) COVID-19. Within this post-COVID-19 cohort, incidence of diabetes over 6 months was lower in patients with mild disease (1.1%) compared with those with moderate/severe disease (4.1%) [8]. Moreover, these authors used a control group of subjects with prior influenza infection matched for disease severity and other pertinent variables such as age, gender, ethnicity, obesity, family history of diabetes. Over 6 months, the risk of new-onset diabetes

Table 1: Retrospective studies that examined incident diabetes as the only outcome in the post-COVID-19 period.

Reference, country	Setting/data source	Follow-up	Patients' characteristics and groups	Results	Comments
1.Xie and Al-Aly [6] USA	National health care databases of the department of Veterans Affairs of patients having positive COVID-19 from 3/1/2020 to 09/03/2021	from 30 days post-COVID-19 to a median follow-up of 352 days (IQR 245-406)	Post- COVID-19 group (n=181,280, mean age 61 years, 88% men, 76% Whites, 17% Blacks), contemporary control group (n= 4,118,441)	↑ risk of type 2 diabetes in the post-COVID-19 group vs contemporary control group HR 1.40, 95% CI 1.36-1.44). ↑ risk of anti-hyperglycemic agents in post-COVID-19 group HR 1.85 (95% CI, 1.75-1.92)	Risk of incident diabetes increased in a graded fashion according to the severity of COVID-19
2.Wander et al. [7] USA	Veteran Affairs administrative data of patients with positive COVID-19 from 03/01/2020 to 03/10/2021	mean 193 days (range 32-456 days)	Post-COVID-19 group n=126,710, mean age 56 years, 87% men, 69% Whites, 21% Blacks vs non-COVID-19 matched control group n=2,651,058	↑ risk of diabetes in the post-COVID-19 group vs control group OR 1.95 (95% CI, 1.80-2.12) at end of follow-up in men. Risk of diabetes is not significant in women.	In men, risk of diabetes in the post-COVID-19 group was higher in Blacks vs non-Blacks (OR 1.61, 95% CI, 1.25-2.09), and Latinx vs non-Latinx (OR 1.49, 95% CI, 1.31-1.70)
3.Birabaharaban et el. [8] US	Health research network database that aggregates US national health records	6 months	Post-COVID-19 group mild (n=53,236) and moderate/severe disease (n=394,667) vs matched control group with influenza	RR of incident diabetes in mild COVID-19 vs mild influenza 1.54 (1.46-1.62). RR in moderate/severe COVID-19 vs moderate/severe influenza 1.46 (95% CI, 1.26-1.69)	After excluding patients who used steroids during COVID-19, RR remained similar in moderate/severe disease 1.42 (95% CI 1.26-1.69), but was attenuated (but still significant) in mild disease 1.22 (95% 1.14-1.29)
4.Rathmann et al. [9] Germany	Nationwide database.	Median (IQR) follow-up 119, 0-210) days	Post-COVID-19 outpatients, n=35,865, mean age 42.6 years, 45.6% women Control group had history of upper respiratory infection	↑ risk of type 2 diabetes in the post-COVID-19 group vs control group Incident RR 1.28 (95% CI, 1.05-1.57)	The increase in incidence of other types of diabetes in the post-COVID-19 group was not significant. Subjects who received GC in the first 30 after COVID-19 were excluded.

Abbreviations: IQR: Inter-Quartile Range, HR: Hazard Ratio, RR: Risk Ratio, CI: Confidence Interval, URI: Upper Respiratory Infection, GC: Glucocorticoids.

was still increased in the post-COVID-19 group compared with the control influenza group in both mild (risk ratio 1.54) and moderate/severe disease (risk ratio 1.46) (table 1). After exclusion of patients who received steroids for COVID-19, the increased risk of incident diabetes remained elevated in patients with moderate/severe COVID-19 (risk ratio 1.42, 95% CI, 1.13-1.80), but was somewhat attenuated, yet still statistically significant, in patients with mild disease (risk ratio 1.22, 95% CI 1.14-1.29).

In a relatively smaller retrospective study from Germany, Rathmann et al. [9] compared the incidence of diabetes in outpatients with documented COVID-19 (n=35,865, mean age 42.6 years, 45.6% women) with matched control subjects who had upper respiratory infections unrelated to COVID-19. To avoid the confounding effects of glucocorticoids therapy, patients who received such therapy within 30 days after COVID-19 diagnosis were excluded [9]. After a median duration of follow-up of 119 days after COVID-19 diagnosis, the incidence rate ratio of type 2 diabetes was 1.28 (95% CI 1.05-1.57, p=0.016) compared with the control group. Moreover, there was a trend towards increased incidence of other types (unspecified) of diabetes that did not reach statistical significance 1.17 (95% CI, 0.80-1.71; p=0.417) [9]. In the studies of Birabaharan et al. [8] and Rathmann et al. [9], the finding of greater incidence of diabetes after SARS-CoV-2 infection compared with non-SARS-CoV-2 upper respiratory infections or influenza supports the notion that diabetes may be a specific complication of COVID-19 and not merely the result of general morbidity after viral illness.

Risk of type 1 diabetes after COVID-19 recovery

There is only one available retrospective study that examined incident type 1 diabetes after COVID-19 recovery. Thus, in a cohort of 365,080 persons aged less than 35 years, McKeigue et al. [10] in Scotland examined the risk of development of type 1 diabetes 30 days after infection with COVID-19. This cohort was followed approximately 18 months (from March 2020 to November 2021), and the rates of incident of type 1 diabetes was compared with control subjects matched for age, sex and general practice [10]. These researchers did not find significant association between prior COVID-19 infection and incident type 1 diabetes from 30 days post-infection up to end of follow-up (rate ratio 0.88, 95% CI 0.63-1.23) [10]. Meanwhile, during the 30 days following COVID-19 infection, there was more than 2-fold increase in incident type 1 diabetes, rate ratio 2.62 (95% CI 1.81-3.79) [10]. It should be emphasized that this study suffers from several limitations. First, it was not peer-reviewed and therefore published as a pre-

print publication [10]. Second, complete description of patients' demographics and other characteristics were not provided [10]. Third, the authors did not control for relevant covariates that may affect rates of incident diabetes. Clearly, more studies in different countries are needed to evaluate risk of new-onset type 1 diabetes in the post-COVID-19 period.

Risk of incident diabetes after COVID-19 in the pediatric population

Barret et al. [11] conducted a retrospective analysis of 2 databases derived from 2 commercial health care claims in the US, IQVIA (n=80,893) and HealthVerity (n=439,439), of patients aged less than 18 year who were infected with COVID-19. Overview of this study is summarized in table 2. The authors compared the incidence of diabetes (of any type) more than 30 days after COVID-19 diagnosis in these 2 health care systems with age and sex-matched subjects without COVID-19, and another control group of patients who had pre-pandemic upper respiratory infection clearly unrelated to COVID-19 [11]. Diabetes incidence (approximately 94% of cases were diagnosed as type 1 or type 2 diabetes) over 1 year was significantly higher among those with history of COVID-19 than among those without COVID-19 in both databases; HR 2.66 (95% 1.98-3.56) in IQVIA and 1.31 (95% CI 1.20-1.44) in HealthVerity [11]. In addition, risk of diabetes was higher compared with patients with non-COVID-19 upper respiratory infection; HR 2.16 (95% CI 1.64-2.86). The latter results are in agreement with those recorded in the adult population [8,9]. Furthermore, the increased risk of diabetes was similar across age groups and both sexes [11]. Interestingly, the proportion of patients who presented with diabetic ketoacidosis at or around time of diabetes diagnosis was higher (40-48%) in the post-COVID-19 group than the other 2 comparison groups (14-35%) [11]. Unfortunately, this study of young population did not report new-onset type 1 diabetes and type 2 diabetes separately.

Alterations of glycemic profile in the post-COVID-19 period

Montefusco et al. [12] examined patterns of continuous glucose monitoring (CGM) in a small subgroup of patients (n=10) who recovered from COVID-19 (after a mean ± SD, 62.0±6.5 days after hospital discharge). These investigators found persistence of abnormal 24-h glucose profile in the post-COVID-19 group compared with healthy control subjects. These abnormalities were represented by higher nadir, postprandial and mean blood glucose levels in the post-COVID-19 patients [12]. Moreover, they found that patients who recovered from COVID-19 had greater insulin resistance and beta-cell hyperstimulation compared with healthy control subjects. Therefore, these results suggest that worsening insulin resistance might persist for approximately 2-6 months after recovery of COVID-19.

Mechanisms of glycemic alterations and diabetes in the post-COVID-19 period

Mechanisms of development of diabetes in the post-acute phase of COVID-19 are not fully understood, but they are likely multifactorial. Potential mechanisms are discussed below.

Cytokine release

It is well-established that COVID-19 is associated with increase release of cytokines, which is in its extreme form causes cytokine storm. In the meantime, increase cytokines may lead to insulin resistance [13,14]. Montefusco et al. [12] found that patients who recovered from COVID-19 (n=10) exhibited significant increase in circulating levels of 10 cytokines compared with healthy control individuals [12]. This cytokine upregulation was associated with increased insulin resistance and hyperglycemia as measured by CGM [12]. Thus, these data suggest that hyperglycemia in patients who recovered from COVID-19 might be mediated in part by persistent increase in cytokines. In support of this notion, the observation that COVID-19 patients who received tocilizumab, a drug that lowers the cytokine interleukin 6 (Il-6), also showed a greater reduction in glycemic levels at the time of hospital discharge compared with patients who did receive tocilizumab [12].

Direct invasion of pancreatic β-cells by SARS-CoV-2

Many studies have shown that pancreatic β-cells express the receptors of SARS-CoV-2, namely angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease 2 (TMPRSS2) [15]. Muller et al. [15] have demonstrated that SARS-CoV-2 can infect human exocrine and endocrine pancreatic cells in culture and in post-mortem specimens of 4 patients who died of COVID-19. This infection was associated with reduced numbers of insulin-secretory granules in β-cells and impaired glucose-stimulated insulin secretion [15]. In another *in vitro* study, Tang et al. [16] showed that pancreatic β-cells underwent trans-

Table 2: Risk of incident diabetes after COVID-19 in the pediatric population.

Reference, country	Setting/data source	Follow-up	Patients' characteristics and groups	Results	Comments
Barrett et al. [11] USA	2 medical claims databases: IQVIA and HealthVerity of pediatric population (<18-year-old)	from 30 days after COVID-19 infection. Follow-up IQVIA: 26 months (Jan 29, 2019-March 31, 2021), HealthVerity 32 months (December 1, 2018-Huly 31, 2021)	Post-COVID-19 group (IQVIA n= 80,893) and HealthVerity (n= 439,439). Mean age ~12 years, 50% men. 2 comparison non-COVID-19 infected groups, one without URI and another URI unrelated to COVID-19	↑ risk of diabetes in the post-COVID-19 group HR 2.66 (95% 1.98-3.56) in IQVIA and 1.31 (95% CI 1.20-1.44) in HealthVerity vs non-COVID-19 infected group. HR 2.16 (95% CI 1.64-2.86) vs group with non-COVID-19 URI in IQVIA	Non-COVID-19 related URI was not associated with increased diabetes risk. Higher percentages of post-COVID-19 patients presenting with DKA vs control groups (40-48% vs 14-35%)

Abbreviations: HR: Hazard Ratio, URI: Upper Respiratory Infection, DKA: Diabetic Ketoacidosis.

differentiation upon SARS-CoV-2 infection i.e. they demonstrated a lower expression of insulin and a higher expression of markers pertaining to α- and acinar cells, including glucagon and trypsin-1 [16]. Hence, β-cell invasion and trans-differentiation by SARS-CoV-2 could potentially contribute to development of new onset diabetes.

Conclusions and current needs

Overall, there is consistent data derived from retrospective cohort studies showing increased incidence of type 2 diabetes in the 6-12 months following recovery from COVID-19. The available cohort studies are large and representative in most cases of the general population in many countries. The adequate size of some of these investigations allowed subgroup analysis. The latter suggested that the following subgroups of subjects are particularly vulnerable to incident diabetes after COVID-19: people older than 65 years, black and non-white race, obesity, presence of pre-diabetes, hypertension, dyslipidemia, and cardiovascular disease. Importantly, these studies have shown that incidence of diabetes after COVID-19 may be greater than after other types of respiratory infections. However, available studies are mainly retrospective prone for misdiagnosis of diabetes, inability to specify its type with certainty, and incompleteness of electronic medical records. Despite serious attempts to match post-COVID-19 patients with control subjects, unmeasured residual confounding variables having impact on incident diabetes may have persisted. In addition, follow-up periods are relatively short. Thus, the natural history of post-COVID-19 diabetes is unclear. Nevertheless, the available quality of data is sufficiently strong to alert physicians and patients of increased diabetes risk after clinical recovery from COVID-19, particularly in the susceptible subgroups of individuals mentioned above. Therefore, closed surveillance and more frequent screening for diabetes are warranted during the post-COVID-19 period for timely diagnosis and treatment.

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