JOURNAL OF INSURANCE MEDICINE

J Insur Med 2024;51:4–7

REVIEW

Diabetes Following COVID-19 Infection: Is It Common?

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New-onset diabetes mellitus following COVID-19 infection has been frequently reported. This article will review the evidence that supports this observation and provide an opinion about its validity and relevance to insured cohorts.

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Many COVID-19 survivors report protracted symptoms, sometimes lasting 3 years or more. These are collectively called post-acute sequelae of SARS-CoV-2 infection (PASC), or long Covid.[1–4] Further, several established diseases appear to be diagnosed more frequently following COVID-19 infection. Cardio-pulmonary disorders predominate but reports of new-onset diabetes mellitus have also emerged. While early reports focused on hospitalized patients, more recent analyses suggest that diabetes may also develop in non-hospitalized individuals, who constitute the vast majority of COVID-19 survivors.

NEW-ONSET DIABETES MELLITUS

In the early months of the COVID-19 pandemic, it became evident that diabetes mellitus was an important risk factor for both morbidity and mortality. As the pandemic evolved, reports of de novo diabetes suggested that a bi-directional risk might exist—while diabetes was clearly a risk factor for severe COVID-19 infection, the latter might, in turn, precipitate de novo diabetes. These early retrospective studies, mostly conducted in hospitalized adult and pediatric cohorts in China, Europe and the US, suggested that the incidence of both type 1 and type 2 diabetes was increased. An August 2020 systematic review and meta-analysis of 8 of these retrospective cohorts, with 3711 hospitalized subjects, reported 492 new diagnoses of diabetes, for a 14% incidence rate.[5] While an impressive number, the follow-up periods were short, and multiple confounders were present, such as the stress response of hospitalization and treatment with glucocorticoids. Further, the lack of a control group and the likely inclusion of pre-morbid undiagnosed diabetes raised questions about the contribution of SARS-CoV-2 infection.

In 2021-22, multiple studies described similar findings.[6–19] In contrast to earlier reports, both inpatient and outpatient cohorts were included, with follow-up periods of 3 months to a year. The incidence of both types 1 and 2 diabetes was increased, although the observation was not entirely consistent; 2 studies reported no increased risk, after 30 days[14] and beyond 3 months.[17] Two systematic reviews of these studies came to similar conclusions.[20,21] In the first, an analysis of 9 studies and over 40 million participants in the US and Europe, the overall incidence of diabetes after COVID-19 infection was 15.53 cases (CI 7.91-25.64) per 1000-person-years.[20] This contrasts with the US 2021 crude estimate of 5.9 new diagnoses of diabetes per 1000 adults, age 18 or older. The pooled risk of developing diabetes after COVID-19 infection was elevated (RR 1.62; CI 1.45-1.80), with risk of type 2 (RR 1.70) slightly higher than that of type 1 (RR 1.48). Risk was evenly spread across all age groups, higher among hospitalized individuals, and highest in the first 3 months following infection. When compared to the incidence of diabetes following other respiratory infections, the risk was smaller but remained slightly elevated (RR 1.17).

The second meta-analysis provided similar results: it analyzed 8 studies of 47 million subjects with mean follow-up of 3 months to 1 year.[22] Median age was 43 years, and 50% were female. The risk of incident diabetes was increased (HR 1.66; CI 1.38-2.00), virtually identical to the previous systematic review. Risk was not modified by age or sex. A sub-analysis showed a higher risk in the North American (HR 1.77) vs European studies (HR 1.33).

Both these systematic reviews have limitations. In each review, the selected studies relied on electronic health record information to establish the diagnosis of both diabetes and COVID-19 infection. Reliance on diagnostic codes, prescription records, laboratory results, and tallies of clinical visits to establish disease incidence is intrinsically error prone. Thus, misclassification bias, based on incorrect allocation to exposure (COVID-19) and/or outcome (new-onset diabetes) groups, is a substantive problem. Another limitation is the lack of meticulous exclusion of diabetes. The lack of careful exclusion of pre-existing diabetes is another concern. It is worth noting that the US Centers for Disease Control and Prevention (CDC) estimates that 23% of the US population has undiagnosed diabetes.[22] Healthcare visits for COVID-19 infection may have simply prompted earlier diagnoses. Numerous other limitations exist including different study periods, different follow-up times, different viral variants, and the effect of antiviral treatments and vaccination. Indeed, in both systematic reviews, the authors recognized high study heterogeneity; this may detract from the summative result provided.

These studies provided a perspective for the first year after COVID-19 infection. More recently, a 2023 study of 138,000 US veterans reported that the risk of diabetes remained elevated up to 2 years following COVID-19 infection.[23] After the first 6 months, when risk was similar to that reported in both systematic reviews (RR 1.61), the risk in an outpatient cohort decreased but remained slightly elevated at 2 years (RR 1.13). Similarly, in the hospitalized cohort, the RR decreased over time (RR 7.40 at 3 months, 1.53 at 2 years). The sustained elevated risk of diabetes at 2 years in the non-hospitalized cohort contrasted with the return to baseline for the majority of post-COVID sequelae. It merits attention that the Veteran Administration population, being predominantly older and >80% male, may be at higher risk of developing diabetes. Further, multiple confounders may be at play; this population has a high prevalence of illnesses that are risk factors for both COVID-19 infection and diabetes. Teasing out the contribution of COVID-19 will always be a challenge.

IS THERE A PLAUSIBLE PATHOGENESIS?

Different explanations have been advanced to explain the increased incidence of diabetes following COVID-19 infection. Pre-COVID-19 unrecognized diabetes has already been mentioned. Lack of exercise and poor dietary habits during the sustained lockdowns that characterized the early months of the pandemic, may have contributed to the pre-diabetic pool. Similarly, protracted recovery periods following COVID-19 infection, by reducing exercise and favoring weight gain, may have also contributed. None of these factors are unique to COVID-19 infection; they are shared by other infectious processes. However, in the studies previously described, the incidence of diabetes goes beyond the incidence described for other respiratory illnesses, suggesting that SARS-CoV-2 infection confers an increased risk. Pancreatic beta-cell damage due to cellular invasion by SARS-CoV-2 or due to an autoimmune response has also been proposed, but there is uncertainty about both. Similarly, the persistence of SARS-CoV-2 in adipose tissue might promote insulin resistance – the central mechanism of type 2 diabetes. Once again, there is no clarity. However, the trend to normoglycemia over time suggests that a unique COVID-19 mechanism may be operative. It is also possible, indeed likely, that multiple mechanisms are at play. In this mix, the attributable risk to SARS-CoV-2 infection is difficult to sort out. In the meantime, the acronym NODAC (new-onset diabetes after COVID-19) has been proposed to describe diabetes that is diagnosed after COVID-19.[24] It is hoped that by creating stringent criteria for diagnosis of NODAC, further investigation will sort out the precise pathogenesis and ultimately quantify the proportion of risk that can be ascribed directly to SARS-CoV-2 infection, if any.

RELEVANCE TO INSURED COHORTS

Are these findings relevant to an insured population? Insured cohorts, being healthier and with fewer co-morbidities are unlikely to be at the same risk as the cohorts described in studies to date. They are also more likely to be vaccinated; a small study of vaccination suggests that it reduces the risk of post-COVID incident diabetes.[25] So, while the risk of de-novo diabetes following COVID-19 in a general population may be elevated, it is unlikely that insured cohorts will be similarly affected. However, the post-COVID-19 landscape is unsettled; the risk of diabetes will be under scrutiny for the foreseeable future.

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