# ASSOCIATION BETWEEN COVID-19 INFECTION AND NEW-ONSET DIABETES IN A TERTIARY CARE HOSPITAL IN KATHMANDU

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## ABSTRACT

In severe acute respiratory syndrome coronavirus 2 infections, reduced numbers of insulin secretory granules in beta cells and impaired glucose-stimulated insulin secretion have been observed, with insulin resistance and the onset of diabetes in them. This study was conducted to find the association between COVID-19 infection and new-onset diabetes. This was a cross-sectional study conducted in the Department of Internal Medicine at Nepal Medical College Teaching Hospital, for a duration of 6 months (July to December 2021). A total of 38 new-onset diabetes patients with a confirmed history of COVID-19 infection were enrolled in the study using a non-probability convenient sampling technique. Ethical clearance was taken from the Research and Institutional Review Committee, Nepal Medical College Teaching Hospital (Reference No.068-077/078). Venous blood was collected and fasting blood glucose, post-prandial blood glucose, and HbA1c were measured. Data were analyzed in the Statistical Package for Social version 20.0. Analytical data were compared using Z- test for the parametric values and the Chi-Square test for the nonparametric values. Statistical significance was defined as a p-value of less than 0.05. As per clinical severity, 22 had mild, 13 had moderate and three had severe COVID-19 infection. The mean fasting blood sugar was 169.84 ± 40.72 mg/dl and the mean postprandial blood sugar was 249.92 ± 72.46 mg/dl. The mean HbA1c was 7.92 ± 1.11%. Out of 38 patients, 36 had a history of systemic steroid use and hyperglycemia was significantly associated with steroid use (Z=1.97, P=0.024).

## KEYWORDS

COVID-19, diabetes mellitus, new onset

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## INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), is a major endemic global challenge with ongoing incidence.[1] The clinical spectrum of SARS-CoV-2 infection ranges from mild to critically ill cases, manifesting as asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and even death.[2] Although most infected people are thought to have a favorable prognosis, with the people with chronic diseases commonly seen in elderly people, such as hypertension, diabetes mellitus, cerebral vascular disease, and their susceptibility conditions, may lead to poor clinical outcomes, in time of pre-pandemic.[3]

Several studies have suggested that adults face an increased risk of diabetes diagnosis after contracting COVID-19. The mechanism for diabetes post COVID-19 is not well understood. There are two suggested pathways; one direct effect of the virus in the pancreas and next impact of the virus to the immune system which causes the insulin resistance. The human pancreas is a target of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Following SARS-CoV-2 infections, reduced numbers of insulin secretory granules in beta cells and impaired glucose-stimulated insulin secretion have been observed. SARS-CoV-2 may damage beta cells by triggering pro-inflammatory cytokines. Pro-inflammatory pathways leading to chronic low-grade inflammation in the adipose tissue play an important role in the pathogenesis of insulin resistance and the onset of diabetes. However, it is unclear whether such metabolic alterations are transient or whether individuals with COVID-19 have an increased future risk of persisting diabetes.[4] The incidence of type 2 diabetes in the subjects affected by SARS-CoV-2 vary, depending on the median age, the severity of illness, the location of the study population, and the method of testing.[5]

Nepal experienced a surge of COVID-19 infection in the year 2021. As of May 2022, a total of 979,140 cases and 11,951 deaths associated with COVID-19 have been reported in Nepal.[6] A study done in the United States shows rates of incident diabetes, hypertension and hyperlipidemia was higher than those before COVID-19. The highest post-infection odds were for diabetes (odds ratio [OR]= 2.35), followed by hypertension (OR=1.54), the benchmark diagnoses (OR= 1.42), and hyperlipidemia (OR=1.22). After adjustment, the risk of new-onset diabetes versus benchmark diagnosis after COVID-19 infection was elevated significantly (OR=1.58, or a 58% higher risk), but the risks of hypertension and hyperlipidemia weren't. Although post-infection diabetes risk was higher among unvaccinated participants (OR=1.78) than among their vaccinated counterparts (OR, 1.07), the interaction between vaccination and diabetes diagnosis was not statistically significant (OR=0.59).[7] It is important to understand the potential link between COVID-19 infection and new-onset diabetes mellitus, to develop an effective management and prevention strategies for this population. This study aims to look into the profile of patients with diabetes after COVID-19 infection which will help us to identify the risk of developing the disease.

## MATERIALS AND METHODS

A hospital-based observational study was carried out in the Department of Internal Medicine at Nepal Medical College Teaching Hospital from July to December 2021 after taking the ethical clearance from the Institutional Review Committee, Nepal Medical College Teaching Hospital (Reference No. 068-077/078). All the patients with a new diagnosis of diabetes mellitus were asked about the history of COVID-19 infection (either antigen or rt-PCR). If they have history of a confirmed COVID-19 infection were enrolled in the study. Demographic profile of the patient and clinical severity of the COVID 19 noted. Medical history with a particular focus on steroid use was noted. The time of evaluation was 2 months to 6 months after COVID-19 infection, those patients who were diagnosed during treatment of COVID-19 were excluded. A total of 38 individuals who gave their written consent were included in the study by using non-probability convenient sampling technique. Body mass index (BMI) was measured from all participants. A usual investigational workup for diabetes was done by collecting venous blood samples for, fasting blood sugar, post-prandial blood sugar and, HbA1c. The values were noted. These patients were then followed according to the usual follow up for diabetes. Data were entered and analyzed in the Statistical Package for Social version 20.0. Analytical data were compared using Z-test for parametric values and Chi-Square test ($X^2$) for nonparametric values. Statistical significance was defined as a p-value of less than 0.05.

## RESULTS

There were total 38 study participants included in the study. The male-to-female ratio was 1.7:1.

The mean age of the patients was 51.5 ± 14.8 years. The mean BMI was 25.3 ± 3.9. Among them, 14 patients had fa family history of diabetes mellitus. Twenty-four of the patients had a history of steroid use during COVID-19 infection (Table 1). Out of 14 females, three of them had history of gestational diabetes and one had a history of polycystic ovary disease (PCOS). As per clinical severity, 22 had mild, 13 had moderate and three had severe COVID-19 infection (Fig. 1). Among patients with mild COVID-19 severity, 91.0% of them had a history of steroid use.

Among study population, 34.0% of them were more than 60 years and had developed diabetes. Age more than 60 was significantly associated with the development of diabetes (z = -2.84, p = 0.004). There were 24 males and 14 females, however, sex was not significantly associated with post COVID-19 diabetes ($X^2$ = 2.63, p=0.104). The mean fasting blood sugar was 169.84 ± 40.72 mg/dl and the mean postprandial blood sugar was 249.92 ± 72.46 mg/dl. The mean HbA1c was 7.92 ± 1.11%.

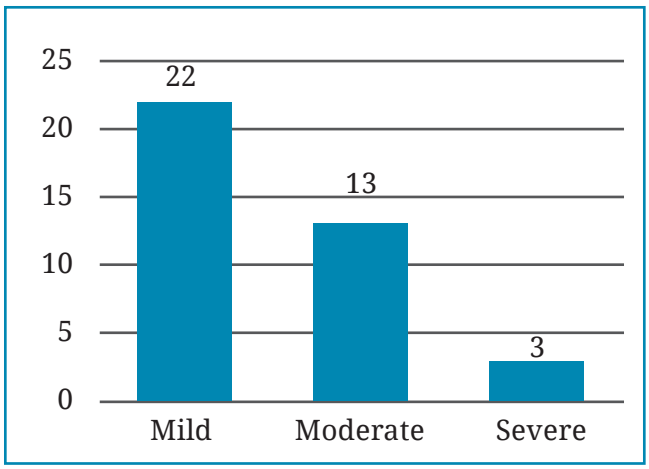


**Fig. 1:** Severity of COVID-19 among study participants

Out of 38 patients, 36 had history of systemic steroid use and hyperglycemia was significantly associated with steroid use (Z = 1.97; P = 0.024). Family history of diabetes was present in 14 of the participants however, it was not significantly associated with diabetes (Z = 1.19; p = 0.233). Three out of 14 females had gestational diabetes mellitus (GDM) which was significantly associated with hyperglycemia (Z = -1.90; p = 0.029). Asian BMI cutoff value of 23, which is classified as obesity, was not associated with diabetes (Z score 0.79; p = 0.214). Regarding the clinical severity of the disease, 22 patients had mild severity, 13 patients had moderate severity and 3 had severe disease severity. Moderate to severe disease was not significantly associated with diabetes ($X^2$ = 0.947; p = 0.33) Regarding profession, 15 were office workers, 10 of them had semi-mobile jobs, six were housewives, three retired from service, and four of them were manual labor. Using chi-square distribution table, it was seen that office workers were more likely to develop diabetes if they got COVID infection ($X^2$ = -23.08; p = 0.001).

## DISCUSSION

Diabetes mellitus is a well-known risk factor for worse clinical outcomes in patients with

**Table 1: Study population characteristics**

| Characteristics | Values | |
|---|---|---|
| **Age** | 51.5 ± 14.8 years | |
| **Sex** | Male: 24<br>Female: 14 | $X^2$ = 2.63; p = 0.104 |
| **BMI** | 25.3±3.9 kg/m$^2$ | Z score 0.79; p = 0.214 |
| **Family history of DM** | 14 | Z = 1.19; p =0.233 |
| **COVID-19 severity** | Mild: 22<br>Moderate: 13<br>Severe: 3 | $X^2$ = 0.947; p = 0.33 |
| **Steroid use** | 36 | Z = 1.97; P = 0.024 |
| **Profession** | Office works: 15<br>House wives: 4<br>Manual laborer: 6<br>Retired: 3<br>Semi-mobile: 10 | $X^2$ = -23.08; p = 0.001 |

COVID-19. However, the relationship between these two entities seems to be bidirectional. Infection with SARS-CoV-2 in the setting of diabetes mellitus (DM) initiates a series of cascading effects that result in increased mortality. Infection with COVID-19 predisposes infected individuals to hyperglycemia, leading to hyper-glycosylation of ACE2 and increased viral proliferation. Worsening of hyperglycemia induces inflammation, endothelial dysfunction, and thrombosis via the generation of oxidative stress driving the dysregulation of glucose metabolism and hypercoagulability further. Severe infection in individuals predisposed to vasculopathy and impaired immunity may accentuate thrombotic and ischemic complications associated with multiorgan failure and increased mortality rates. COVID-19 has been shown to have a significant impact on glucose metabolism which increases the risk of developing diabetes mellitus in some patients. Several studies have identified risk factors that can increase the likelihood of developing diabetes after COVID-19 infection.[12-14] In a meta-analysis by Zhang et al,[13] the incidence of diabetes after COVID-19 was 15.53 (7.91–25.64) per 1000 person-years, and the relative risk of diabetes after COVID-19 infection was elevated [RR 1.62 (1.45–1.80)]. The relative risk of type 1 diabetes was RR = 1.48 (1.26 – 1.75) and type 2 diabetes was RR = 1.70 (1.32 – 2.19), compared to non-COVID-19 patients.

In our study too, hyperglycemia was seen among COVID-19 patients, mostly in the age above 60 years. Age more than 60 was significantly associated with development of diabetes in our study. In our study mean age of the patients was 51.53 years. However there are other studies which was showing a continuous relationship of age with new-onset diabetes post COVID-19 infection.[16]

In a study done by Holman *et al*,[7] the relative risk of diabetes in different gender groups. It was seen that males had a slightly higher incidence compared to female counterparts (males: RR=2.08 [1.27–3.40]; females: RR=1.99 [1.47–2.80]). In our study, there was no difference in the incidence of diabetes in the male and female populations. However, in females, 3 out of 14 females had gestational diabetes mellitus which was significantly associated with hyperglycemia. No clear explanation could be given about this association. In our study, office workers were more likely to develop diabetes if they got Corona virus infection. Other than stress and obesity which is common in office workers no other obvious explanation could be given for this association.

Obesity is a well-known risk factor for both diabetes and severe COVID-19. A study conducted in United States[14] found that patients with obesity who were hospitalized with COVID had a higher risk of developing diabetes than non-obese patients. Contrast to this study, in our study obesity was not significantly associated with the development of diabetes however it is worth noting that our study includes both the groups of patients hospitalized and not hospitalized.

Patients with a family history of diabetes are more likely to develop diabetes after a COVID-19 infection. A study conducted in China found that patients with a family history of diabetes had a higher risk of developing diabetes after COVID-19 infection than those without a family history.[13] In contrary to the study done in China, our study did not show any significance between family history of diabetes with post COVID-19 new-onset diabetes.

Patients with more severe Corona virus infections are more likely to develop diabetes. A study conducted in the United States found that patients who were hospitalized with COVID-19 and requiring mechanical ventilation had a higher risk of developing diabetes than patients who did not require mechanical ventilation.[14] Our study, however, did not reveal that COVID-19 severity was associated with new-onset diabetes. We did not have any data on pre-admission condition of the patients but a study done by Palaiodimos *et al*,[22] found that patient with metabolic syndrome who were hospitalized with covid had a higher risk of developing diabetes than patients without metabolic syndrome. We are unable to comment on this regard as pre-COVID-19 data was not available.

Steroid-induced hyperglycemia is very common in hospitalized patients. A previous study had shown that 53–70% of individuals without diabetes develop steroid-induced hyperglycemia.[23] An Australian study of 80 hospitalized people without diabetes reported that 70.0% of subjects had at least one blood glucose measurement of ≥10 mmol/L.[24] A meta-analysis of 13 studies showed that overall, 32.3% of people developed glucocorticoid-induced hyperglycemia, and 18.6% developed diabetes.[25] Use of steroids, particularly following the publication of the RECOVERY trial with the use of dexamethasone in people admitted to the hospital with COVID-19, may therefore also be associated with an increased risk of developing diabetes, which again could be directly related to steroid-induced abnormalities with delayed or blunted recovery of β-cell damage.[26] Our

study also highlights the fact that one of the mechanisms for developing high blood sugar post- Corona virus infection was the use of systemic steroid, as hyperglycemia was significantly associated with the steroid use.

Patients with severe COVID-19 were at higher risk of diabetes after COVID-19. The risk of diabetes was highest in the first 3 months after COVID-19.[13] These results remained after taking confounding factors into account. Our study though not designed to look into the duration lag between covid 19 infection and diabetes has all the patients presented between 2 months to 6 months post-Corona virus infections.

In conclusion, though there are controversies about the onset of diabetes post covid, there seems to be increasing evidence to suggest this is occurring. Though there is not consensus about what caused it. Our study suggests that systemic steroid use during Corona virus infection may be a risk factor for hyperglycemia besides the age of more than 60. Additionally, gestational diabetes appeared to be a significant risk factor for female patients. The study also highlights the potential increased risk of developing diabetes in office workers who get Corona virus infection. Further research is needed to confirm these findings and explore the mechanism behind these association.

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