Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Endocrine Practice 28 (2022) 191–198

Contents lists available at ScienceDirect

Endocrine Practice

journal homepage: www.endocrinepractice.org

Original Article

SARS-CoV-2 Seroprevalence in Individuals With Type 1 and Type 2 Diabetes Compared With Controls

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ARTICLE INFO

Article history:
Received 28 August 2021
Received in revised form
27 November 2021
Accepted 9 December 2021
Available online 14 December 2021

Key words:
COVID-19
diabetes
obesity
SARS-CoV-2
type 1 diabetes
type 2 diabetes

ABSTRACT

Objective: Data for the association between diabetes and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) susceptibility are conflicting. We aimed to evaluate this association using an analytical cross-sectional study design.

Methods: Study participants were recruited from endocrine clinics of our hospital and belonged to 3 groups: group 1 (type 1 diabetes mellitus [T1DM]), group 2 (type 2 diabetes mellitus [T2DM]), and group 3 (controls). All participants submitted blood samples for SARS-CoV-2 S1/S2 immunoglobulin G antibody test (LIAISON; DiaSorin) and were interviewed for a history of documented infection.

Results: We evaluated a total of 643 participants (T1DM, 149; T2DM, 160; control, 334; mean age, 37.9 ± 11.5 years). A total of 324 (50.4%) participants were seropositive for SARS-CoV-2. The seropositivity rate was significantly higher in the T1DM (55.7% vs 44.9%, $P = .028$) and T2DM (56.9% vs 44.9%, $P = .013$) groups than in the control group. The antibody levels in seropositive participants with T1DM and T2DM were not significantly different from those in seropositive controls. On multivariable analysis, low education status (odds ratio [OR], 1.41 [95% CI, 1.03-1.94]; $P = .035$), diabetes (OR, 1.68 [95% CI, 1.20-2.34]; $P = .002$), and overweight/obesity (OR, 1.52 [95% CI, 1.10-2.10]; $P = .012$) showed a significant association with SARS-CoV-2 seropositivity. The association between diabetes and SARS-CoV-2 seropositivity was found to further increase in participants with coexisting overweight/obesity (adjusted OR, 2.63 [95% CI, 1.54-4.47]; $P < .001$).

Conclusion: SARS-CoV-2 seropositivity, assessed before the onset of the national vaccination program, was significantly higher in participants with T1DM and T2DM than in controls. The antibody response did not differ between seropositive participants with and without diabetes. These findings point toward an increased SARS-CoV-2 susceptibility for patients with diabetes, in general, without any differential effect of the diabetes type.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has affected lives globally for more than a year now. At the time of writing this article, >175.9 million confirmed cases and >3.8 million fatalities have been reported worldwide.[1] Diabetes is estimated to affect 463 million adults, representing 9.3% of the global adult population.[2] It is, therefore, not surprising that diabetes (along with hypertension and obesity) has been commonly reported in patients with COVID-19. A recent meta-analysis of 18 studies reported a pooled prevalence of diabetes among patients with COVID-19 as 11.5% (95% CI, 9.5-13.4).[3] Besides being a common comorbidity, diabetes is associated with an increased risk of severe disease (odds ratio [OR], 2.35; 95% CI, 1.80-3.06) and poor patient outcomes, including mortality (OR, 2.50; 95% CI, 1.74-3.59).[4]

Diabetes has been postulated to increase susceptibility for acquiring severe acute respiratory syndrome coronavirus 2 (SARS-

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; HbA1c, hemoglobin A1C; IgG, immunoglobulin G; OR, odds ratio; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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https://doi.org/10.1016/j.eprac.2021.12.009
1530-891X/

CoV-2) infection through various mechanisms.[5–10] However, data to suggest an increased risk of COVID-19 among patients with diabetes are conflicting. A community-based seroprevalence study performed in rural Bangalore district of India found no association between diabetes and SARS-CoV-2 seropositivity.[11] On the other hand, a hospital-based study from Mumbai, India, that compared demographic factors and comorbidities between reverse transcriptase–polymerase chain reaction (RT-PCR)–positive and RT-PCR–negative cases found a significant association between diabetes and SARS-CoV-2 infection.[12] As many as 7 undetected infected individuals may exist in community for every single RT-PCR–confirmed case; hence, the findings of the latter study may not be generalizable to SARS-CoV-2 infection, as a whole.[11] Furthermore, there are no studies in the literature that have evaluated differences in SARS-CoV-2 susceptibility between individuals with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

Indirect evidence on the question of susceptibility can also be gathered by comparing the prevalence of diabetes in patients with COVID-19 with that in the general population. The estimates have varied from 7.2% to 27.3% in various studies from China, Italy, the United States, and India, which are lesser, equal, or greater than the background prevalence of diabetes in these countries.[13–21] Therefore, based on these data, it is difficult to draw any firm conclusion with regard to disease susceptibility. Moreover, there are 2 major limitations in interpreting these results as surrogates for diabetes susceptibility: (1) there is a lack of clarity or heterogeneity across studies in terms of how diabetes was defined as a comorbidity, and (2) these data are derived from patients admitted in hospital and/or intensive care units and, therefore, likely to be biased in terms of disease severity and the presence of diabetes. A formal study that evaluates and compares prior SARS-CoV-2 infection, both symptomatic and asymptomatic, in persons with and without diabetes, defined using standard biochemical criteria, is, therefore, needed to address this unanswered question.

With this background, we planned this analytical cross-sectional study to evaluate and compare the seroprevalence of SARS-CoV-2 among individuals with (cases) and without diabetes (controls) visiting our hospital, who were enrolled before the onset of the national vaccination program. The study aimed to answer the following important questions: (1) is the risk of acquiring SARS-CoV-2 infection higher in persons with diabetes, (2) is the risk different among persons with T1DM and T2DM, (3) what are the factors associated with an increased risk of SARS-CoV-2 infection, and (4) are humoral immune responses to viral infection comparable among persons with and without diabetes?

Methods

Settings and Study Design

This was an analytical cross-sectional study conducted at a tertiary care center in North India. The study was approved by the institutional ethics committee of All India Institute of Medical Sciences (institutional ethics committee reference number: IEC-110/05.02.2021, RP-40/2021).

Study Population

This study included 3 groups: group 1 (T1DM), group 2 (T2DM), and group 3 (controls—individuals without diabetes). All study participants submitted blood samples between October 1, 2020, and February 27, 2021, as a part of ongoing research projects. Participants in groups 1 and 2 were recruited from general and/or specialty endocrine clinics run by the department. T1DM was defined according to the following clinical definition: (1) age at onset of diabetes of <25 years, (2) persistent insulin requirement within 6 months from the diagnosis of diabetes, and (3) absence of pancreatic calcification and features of insulin resistance such as acanthosis nigricans. The presence of ketosis and pancreatic β-cell autoantibodies was used as an additional supportive feature. T2DM was defined according to the following clinical definition: (1) variable age at onset; (2) presence of obesity, a positive family history, and features of insulin resistance such as acanthosis nigricans; and (3) the lack of insulin dependence for glycemic control, at least early in the disease course. We have an ongoing study involving a cohort of women with hyperglycemia in pregnancy and a comparator group of women with normoglycemia in pregnancy who are followed up in the postpartum period, along with their spouses. These women and their spouses have been included as controls in the present study after confirming that they presently do not have diabetes, that is, fasting plasma glucose levels of <126 mg/dL or 7.8 mmol/L, post 75-g glucose load 2-hour plasma glucose levels of <200 mg/dL or 11.1 mmol/L, and hemoglobin A1C (HbA1c) levels of <6.5% or 48 mmol/mol.

Since the last study sample was collected on February 27, 2021, 2 days before the Indian government initiated vaccination for the high-risk general population, the seropositivity results obtained in this study were not affected by the ongoing vaccination drive.[22]

Study Procedures

Study participants underwent testing for SARS-CoV-2 S1/S2 immunoglobulin G (IgG) antibody, and a past history of documented SARS-CoV-2 infection (confirmed using RT-PCR or rapid antigen test) was recorded. Participants who tested positive for the antibody but had no prior history of documented SARS-CoV-2 infection were classified as having asymptomatic (or mild self-limited) infection. Clinical and anthropometric measurements were performed using standard methods, as described in the previous studies.[23,24] HbA1c levels were measured in all participants; eligible participants without a known history of diabetes underwent the 75-g oral glucose tolerance test using 83.3-g glucose monohydrate, and plasma glucose levels were measured at 0 and 120 minutes.

Study Definitions

Diabetes mellitus was defined as per the American Diabetes Association criteria, that is, fasting plasma glucose level of ≥7.0 mmol/L (126 mg/dL) and/or 2-hour plasma glucose level of ≥11.1 mmol/L (200 mg/dL) and/or HbA1c level of ≥6.5% (48 mmol/mol).[25] Diabetes was diagnosed if any 1 of the 3 criteria was met. Overweight and obesity were defined as a body mass index (BMI) of 25 kg/m^2 to 29.9 kg/m^2 and ≥30 kg/m^2, respectively.[26] Hypertension was defined as a blood pressure of ≥140/90 mm Hg and/or the use of antihypertensive medications.[27] Metabolic syndrome was defined using the International Diabetes Federation criteria, that is, the presence of central obesity (waist circumference of ≥80 cm in females and ≥90 cm in males) along with any 2 of the following: elevated levels of triglycerides (≥1.7 mmol/L [150 mg/dL]), low high-density lipoprotein cholesterol levels (<1.29 mmol/L [50 mg/dL] in females and <1.03 mmol/L [40 mg/dL] in males), elevated blood pressure (≥130/85 mm Hg or receiving treatment for hypertension), and elevated fasting plasma glucose levels (≥5.6 mmol/L [100 mg/dL] or receiving treatment for diabetes).[28] Details of biochemical measurements have been provided as supplementary material (Supplementary Data).

SARS-CoV-2 IgG Antibody Test

IgG antibodies against S1 and S2 proteins of SARS-CoV-2 were detected using an indirect chemiluminescence immunoassay (LIAISON XL autoanalyzer; DiaSorin SpA). The limit of detection for this assay is 3.8 AU/mL, while the measurement range extends up to 400 AU/mL. For samples with levels below and above these limits, values of 3.8 AU/mL and 400 AU/mL, respectively, were entered. For the purpose of this study, an antibody level of ≥15 AU/mL was considered positive and that of <15 AU/mL was considered negative. The intra-assay and interassay coefficients of variation for the assay derived from quality control samples were 5.0% and 8.4%, respectively.

Sample Size Calculation

There were no data on the proposed research questions to inform the sample size calculation at the time of drafting this study. Therefore, we proposed a sample size of 600 (150 in group 1, 150 in group 2, and 300 in group 3) to evaluate the study objectives.

Statistical Analysis

Stata 15.0 (StataCorp) was used for statistical analyses. Data are presented as number (%), mean ± standard deviation, or median and interquartile range (q25-q75), as appropriate. For comparison of qualitative variables between 2 groups, the Pearson χ^2 test was used. Normally distributed quantitative variables were compared using the *t* test, whereas the Wilcoxon rank sum test was used for comparing quantitative variables that were not normally distributed. We used both univariate and multivariable stepwise logistic regression analyses to determine factors associated with SARS-CoV-2 seropositivity. For this analysis, the T1DM and T2DM subgroups were combined into a single group, that is, diabetes. We included all predictors (age, sex, employment status, education status, diabetes, overweight/obesity, hypertension, and metabolic syndrome) taken in the univariate analysis in the backward stepwise logistic regression (multivariable) analysis, with an inclusion criterion of $P < .05$ and exclusion criterion of $P > .25$. A separate analysis was performed to evaluate factors associated with SARS-CoV-2 seropositivity in the subset of individuals with diabetes. For this analysis, 2 additional predictors, that is, duration of diabetes and HbA1c levels, were included. To evaluate the association between metabolic parameters (diabetes and overweight/obesity) and SARS-CoV-2 seropositivity, 4 subgroups were created: (1) no diabetes and normal BMI (reference group), (2) no diabetes but overweight/obese (group I), (3) diabetes and normal BMI (group II), and (4) diabetes and overweight/obese (group III). The results were expressed as unadjusted and adjusted ORs (95% CIs). For adjusted analysis, the following covariates that are known to have a bearing on the outcome were accounted: age and sex (model 1), employment and education status (model 2), hypertension (model 3), and all aforementioned covariates combined (model 4). The significance level was set at $P < .05$.

Results

Baseline Characteristics

We evaluated a total of 643 participants (292 males, 45.4%). Of these, 149 participants (72 males, 48.3%) belonged to the T1DM group, 160 (64 males, 40.0%) belonged to the T2DM group, and 334 (156 males, 46.7%) belonged to the control group. The mean age at the time of evaluation was 37.9 ± 11.5 years. Participants with T1DM were younger (32.6 ± 10.6 years vs 35.1 ± 5.3 years, $P < .001$), whereas those with T2DM were older (48.8 ± 14.6 years vs 35.1 ± 5.3 years, $P < .001$) than controls. Participants with T1DM ($P = .025$) and T2DM ($P < .001$) were less likely to be educated till or above the graduation level compared with controls. They were also less likely to be employed compared with controls (T1DM, $P = .121$; T2DM, $P < .001$) (Table 1).

The median duration of diabetes and mean HbA1c levels were 17 years (range, 12-25 years) and 8.8% ± 1.7% (72.4 ± 18.5 mmol/mol), respectively, in the T1DM group and 5 years (range, 3-10 years) and 8.4% ± 2.0% (68.8 ± 22.1 mmol/mol), respectively, in the T2DM group. The mean BMI for study participants was 25.8 ± 4.6 kg/m^2, lower in the T1DM group (22.5 ± 3.7 kg/m^2 vs 26.3 ± 4.2 kg/m^2, $P < .001$) and higher in the T2DM group (27.9 ± 4.6 kg/m^2 vs 26.3 ± 4.2 kg/m^2, $P < .001$) compared with the control group. Overweight/obesity and central obesity were present in 363 (56.5%) and 457 (71.2%) participants, respectively. Hypertension was present in 127 participants (19.8%), and 184 participants (28.6%) had metabolic syndrome (Table 1).

Seroprevalence and Infection Data

A total of 324 participants (50.4% [95% CI, 46.5%-54.3%]) were seropositive for SARS-CoV-2 IgG. A history of documented infection was present in 70 participants (10.9% [95% CI, 8.6%-13.6%]). All participants ($n = 70$) with a history of documented infection were seropositive, whereas a total of 254 (78.4%) seropositive individuals had no history of documented infection, suggestive of asymptomatic (or mild self-limited) disease. The median antibody levels in seropositive individuals ($n = 324$) was 68.4 AU/mL (range, 34.0-109.0 AU/mL) (symptomatic, 91.1 AU/mL [range, 45.1-137.0 AU/mL]; asymptomatic, 63.5 AU/mL [range, 31.8-105.0 AU/mL]) (Table 2).

The seropositivity rate was significantly higher in the T1DM (55.7% [95% CI, 47.3%-63.8%] vs 44.9% [95% CI, 46.5%-54.3%], $P = .028$) and T2DM (56.9% [95% CI, 48.8%-64.7%] vs 44.9% [95% CI, 46.5%-54.3%], $P = .013$) groups than in the control group. The antibody levels in seropositive individuals with T1DM (71.6 AU/mL [range, 31.5-103.0 AU/mL] vs 64.9 AU/mL [range, 34.8-106.0 AU/mL], $P = .893$) and T2DM (68.5 AU/mL [range, 35.0-129.0 AU/mL] vs 64.9 AU/mL [range, 34.8-106.0 AU/mL], $P = .153$) were not significantly different from seropositive controls. The T1DM and T2DM groups did not significantly differ from the control group in terms of a history of documented infection (T1DM, 9.6% [95% CI, 5.2%-15.3%] vs 10.5% [95% CI, 7.4%-14.3%]; $P = .767$; T2DM, 13.1% [95% CI, 8.3%-19.4%] vs 10.5% [95% CI, 7.4%-14.3%]; $P = .385$) (Table 2).

Factors Associated With SARS-CoV-2 Seropositivity in Study Participants

On univariate analysis involving all study participants ($n = 643$), low education status, that is, less than graduation level (OR, 1.49 [95% CI, 1.09-2.03]; $P = .013$), and the presence of diabetes (OR, 1.58 [95% CI, 1.16-2.16]; $P = .004$) were associated with an increased risk of SARS-CoV-2 infection (or seropositivity). Factors such as the presence of overweight/obesity, age of ≥50 years, unemployed status, and the presence of metabolic syndrome also showed an OR of >1.0; however, the association was not statistically significant. On multivariable analysis, the following factors showed a significant association with SARS-CoV-2 infection: (1) low education status (OR, 1.41 [95% CI, 1.03-1.94]; $P = .035$), (2) the presence of diabetes (OR, 1.68 [95% CI, 1.20-2.34]; $P = .002$), and (3) the

Table 1
Baseline Characteristics of Study Participants

Variable	Total ($N = 643$)	Control ($N = 334$)	T2DM ($N = 160$)	T1DM ($N = 149$)
Males	292 (45.4)	156 (46.7)	64 (40.0)	72 (48.3)
P value (vs control)	…	…	.160	.743
Age (y)	37.9 ± 11.5	35.1 ± 5.3	48.8 ± 14.6	32.6 ± 10.6
P value (vs control)	…	…	<.001	<.001
Education, graduation level and above[a]	361 (56.2)	210 (62.9)	74 (46.3)	77 (52.0)
P value (vs control)	…	…	<.001	.025
Employed[a,f]	312 (48.6)	188 (56.3)	52 (32.5)	72 (48.7)
P value (vs control)	…	…	<.001	.121
BMI (kg/m^2)	25.8 ± 4.6	26.3 ± 4.2	27.9 ± 4.6	22.5 ± 3.7
P value (vs control)	…	…	<.001	<.001
Overweight/obese	363 (56.5)	208 (62.3)	118 (73.8)	37 (24.8)
P value (vs control)	…	…	.012	<.001
WC (cm)[b]	90.9 ± 12.2	92.4 ± 10.2	97.9 ± 11.6	79.8 ± 9.0
P value (vs control)	…	…	<.001	<.001
Central obesity	457 (71.2)	263 (78.7)	145 (91.2)	49 (32.9)
P value (vs control)	…	…	.001	<0001
SBP (mm Hg)[c]	122.2 ± 17.8	118.3 ± 14.2	130.7 ± 18.8	122.0 ± 21.2
P value (vs control)	…	…	<.001	.031
DBP (mm Hg)[d]	78.4 ± 10.5	77.6 ± 9.6	81.7 ± 11.2	76.2 ± 11.0
P value (vs control)	…	…	<.001	.167
Hypertension	127 (19.8)	36 (10.8)	63 (39.4)	28 (18.8)
P value (vs control)	…	…	<.001	.016
Metabolic syndrome	184 (28.6)	74 (22.2)	96 (60.0)	14 (9.4)
P value (vs control)	…	…	<.001	.001
Duration of diabetes (y)	11 (5-19)	…	5 (3-10)	17 (12-25)
HbA1c (%)[e]	6.9 ± 2.1	5.4 ± 0.4	8.4 ± 2.0	8.8 ± 1.7
HbA1c (mmol/mol)	52.3 ± 22.7	35.7 ± 4.3	68.8 ± 22.1	72.4 ± 18.5
HbA1c ≥ 8% or 64 mmol/mol	178 (27.9)	…	80 (51.6)	98 (65.8)

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; HbA1c = hemoglobin A1C; SBP = systolic blood pressure; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; WC = waist circumference.
Data are expressed as *n*, %, mean ± SD, or median (q25-q75), as appropriate.
[a] $n = 148$ for the T1DM group.
[b] $n = 159$ for the T2DM group.
[c] $n = 157$ for the T2DM group and $n = 119$ for the T1DM group.
[d] $n = 158$ for the T2DM group and $n = 119$ for the T1DM group.
[e] $n = 155$ for the T2DM group.
[f] Being employed is defined as a person with a source of income, either self or salaried.

Table 2
Seroprevalence and Infection Data in Study Participants

Variable	Total ($n = 643$)	Control ($n = 334$)	T2DM ($n = 160$)	T1DM ($n = 149$)	DM ($n = 309$)
History of documented infection[a] (%, 95% CI)	70 (10.9%, 8.6%-13.6%)	35 (10.5%, 7.4%-14.3%)	21 (13.1%, 8.3%-19.4%)	14 (9.6%, 5.2%-15.3%)	35 (11.4%, 8.0%-15.4%)
P value (vs control)	…	…	.385	.767	.698
Seroprevalence (%, 95% CI)	324 (50.4%, 46.5%-54.3%)	150 (44.9%, 39.5%-50.4%)	91 (56.9%, 48.8%-64.7%)	83 (55.7%, 47.3%-63.8%)	174 (56.3%, 50.6%-61.9%)
P value (vs control)	…	…	.013	.028	.004
Antibody levels, overall (AU/mL)	15.5 (3.8-68.5)	8.2 (3.8-52.3)	24.7 (3.8-82.8)	20.5 (4.7-79.3)	21.6 (3.8-79.3)
P value (vs control)	…	…	.049	.017	.008
Antibody levels, seropositive (AU/mL)	68.4 (34-109)	64.9 (34.8-106)	68.5 (35-129)	71.6 (31.5-103)	70.0 (33.5-112)
P value (vs control)	…	…	.153	.893	.332
Antibody levels, asymptomatic infection (AU/mL)	63.5 (31.8-105)	57.5 (33.1-104)	65.5 (33-109)	64.1 (29-105)	64.5 (31.4-108)
P value (vs control)	…	…	.553	.965	.734
Antibody levels, symptomatic infection (AU/mL)	91.1 (45.1-137.0)	78.3 (38.9-132.0)	105.0 (67.3-181.0)	89.8 (45.1-103.0)	96.7 (60.9-170.0)
P value (vs control)	…	…	.055	.791	.141

Abbreviations: DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
Data are expressed as *n*, %, or median (q25-q75), as appropriate.
[a] $n = 146$ for the T1DM group.

presence of overweight/obesity (OR, 1.52 [95% CI, 1.10-2.10]; $P = .012$) (Table 3). The strength of the association between low education status and SARS-CoV-2 infection increased further after excluding diabetes from the analysis (OR, 1.50 [95% CI, 1.10-2.05]; $P = .012$). Similarly, the association between diabetes and SARS-CoV-2 infection was stronger after excluding education status from the analysis (OR, 1.76 [95% CI, 1.26-2.44]; $P = .001$).

Factors Associated With SARS-CoV-2 Seropositivity in the Subset of Individuals With Diabetes

In the group with diabetes ($n = 309$), factors such as low education status, HbA1c levels (≥8% or 64 mmol/mol, the presence of overweight/obesity, the presence of metabolic syndrome, and the duration of diabetes (≥10 years) showed an OR of >1.0; however,

Table 3
Factors Associated With SARS-CoV-2 Seropositivity in Study Participants

Variable	OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Age (≥50 y)	1.21 (0.77-1.89)	.407	…	…
Sex (male)	0.95 (0.69-1.29)	.735	…	…
Employment status (unemployed)	1.16 (0.85-1.58)	.346	…	…
Low education status	1.49 (1.09-2.03)	.013	1.41 (1.03-1.94)	.035
			1.50 (1.10-2.05)[a]	.012
Diabetes	1.58 (1.16-2.16)	.004	1.68 (1.20-2.34)	.002
			1.76 (1.26-2.44)[b]	.001
Overweight/obesity	1.36 (0.99-1.86)	.055	1.52 (1.10-2.10)	.012
Hypertension	0.92 (0.63-1.36)	.693	…	…
Metabolic syndrome	1.01 (0.72-1.42)	.960	…	…

Abbreviation: OR = odds ratio.
Reference category includes the following: (1) age of <50 years, (2) female sex, (3) employed, (4) education till graduation level and above, (5) no diabetes, (6) normal body mass index (<25 kg/m^2), (7) normotensive, and (8) no metabolic syndrome.
[a] After excluding diabetes from the model.
[b] After excluding education status from the model.

the association for none of these was statistically significant (Table 4). On multivariable analysis, the presence of overweight/obesity showed a significant association with SARS-CoV-2 infection (OR, 1.63 [95% CI, 1.0006-2.66]; $P = .050$).

Effect of Overweight/Obesity on the Association Between SARS-CoV-2 Infection and Diabetes

On the evaluation of the association between metabolic parameters, that is, diabetes and overweight/obesity, and SARS-CoV-2 seropositivity (reference group—normal BMI and no diabetes), the unadjusted OR for SARS-CoV-2 infection in individuals with overweight/obesity but no diabetes (group I) was 1.48 (95% CI, 0.95-2.33; $P = .086$). The unadjusted ORs increased to 1.70 (95% CI, 1.05-2.74; $P = .030$) in individuals with diabetes and normal BMI (group II) and 2.42 (95% CI, 1.50-3.92; $P < .001$) in individuals with diabetes and overweight/obesity (group III). In the fully adjusted model, the ORs increased from 1.52 (95% CI, 0.96-2.38; $P = .072$) in the first group to 1.69 (95% CI, 1.03-2.78; $P = .039$) in the second group and 2.63 (95% CI, 1.54-4.47; $P < .001$) in the third group (Table 5).

Discussion

This study evaluated an important research question related to the susceptibility of SARS-CoV-2 infection among patients with diabetes. The following critical findings emerge from our work: (1) the seropositivity (and, therefore, infection, asymptomatic or symptomatic) rates were higher in participants with T1DM and T2DM than in controls who were sampled during the same time period, (2) the humoral immune response to SARS-CoV-2 (S1/S2 IgG antibody levels) was comparable between seropositive participants with and without diabetes, and (3) the association between diabetes and SARS-CoV-2 infection was found to further increase in participants with coexisting overweight/obesity.

The overall seroprevalence in study participants was 50.4%. The study participants were sampled during the first wave of pandemic in India, before the commencement of the national COVID-19 vaccination program, thus avoiding the confounding effect of vaccine on seropositivity. The national seroprevalence in India was reported to be 24.1% in a recent serosurvey conducted between December 2020 and January 2021.[29] However, there is a marked heterogeneity in the seropositivity rates across states of the country. The state that our study population catered to, that is, Delhi, reported a seroprevalence of 24.7% as early as October 2020, which climbed up to 56.1% in the latest serosurvey conducted in January 2021.[30,31] Thus, the seroprevalence estimates in our study are generally in line with that reported in the general population during the same time period. Nearly 80% of seropositive participants had asymptomatic or mild self-limited disease, whereas another 20% had significant symptoms, warranting a microbiological test and medical intervention. These data are also in agreement with the reported distribution of COVID-19 severity in the general population—80% asymptomatic or mild, 15% moderate-to-severe, and 5% critical disease.[32] Thus, although study participants were recruited from a hospital, they were fairly representative of the general population of Delhi (in terms of seropositivity rate and distribution of disease severity among the infected individuals).

Seroprevalence was significantly higher in participants with T1DM (55.7%) and T2DM (56.9%) than in controls (44.9%) ($P = .028$ and $P = .013$, respectively). On multivariable analysis, the presence of diabetes emerged as a significant factor associated with SARS-CoV-2 infection. These estimates point toward an increased SARS-CoV-2 susceptibility for patients with diabetes, in general, without any differential effect of the diabetes type. The mechanisms for this increased susceptibility could be as follows: (1) defects in innate and adaptive immune system; (2) increased expression of angiotensin-converting enzyme 2, through which SARS-CoV-2 mediates entry into human cells; (3) increased viral replication in hyperglycemic milieu, related to dysregulation of the immune system and inflammatory response; and (4) decreased cytotoxic natural killer cell activity.[5–10] Among individuals with diabetes, factors such as age (≥50 years), glycemic control (HbA1c levels of ≥8% or 64 mmol/mol), and duration of diabetes (≥10 years) were not associated with an increased risk of SARS-CoV-2 infection. However, since these associations were studied in a smaller subgroup ($n = 309$, T1DM plus T2DM), they mainly serve as preliminary observations that require confirmation in a larger study.

The humoral immune response against SARS-CoV-2 S1/S2 spike proteins, measured in terms of antibody levels, was comparable among seropositive individuals with and without diabetes. These findings are in agreement with those reported in a study by Lampasona et al[18] from Italy, in which antibody responses in patients with diabetes ($n = 139$) and previous hospital admission for COVID-19 were found to be comparable to their counterparts without diabetes ($n = 370$). Another study by the same group compared SARS-CoV-2–neutralizing antibody response among patients with ($n = 40$) and without diabetes ($n = 110$) and a history of COVID-19 pneumonia.[33] The neutralizing antibody activity among participants with diabetes was superimposable, in terms of kinetics and extent, to that of patients without diabetes and correlated with the humoral immune response against the SARS-CoV-2 spike protein. These findings suggest that unlike hepatitis B, immunologic response to SARS-CoV-2 is preserved in patients

Table 4
Factors Associated With SARS-CoV-2 Seropositivity in the Subset of Individuals With Diabetes

Variable	OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Age (≥50 y)	0.90 (0.55-1.47)	.672	…	…
Sex (male)	0.92 (0.58-1.45)	.715	…	…
Employed status (unemployed)	0.83 (0.52-1.32)	.433	…	…
Low education status	1.51 (0.96-2.38)	.073	…	…
HbA1c (≥8% or 64 mmol/mol)	1.31 (0.83-2.07)	.253	…	…
Overweight/obesity	1.43 (0.91-2.24)	.124	1.63 (1.0006-2.66)	.050
Hypertension	0.82 (0.50-1.33)	.415	…	…
Metabolic syndrome	1.19 (0.74-1.91)	.464	…	…
Duration of diabetes (≥10 y)	1.04 (0.66-1.64)	.854	…	…

Abbreviations: HbA1c = hemoglobin A1C; OR = odds ratio.
Reference category includes the following: (1) age of <50 years, (2) female sex, (3) employed, (4) education till graduation level and above, (5) HbA1c level of <8% or 64 mmol/mol, (6) normal body mass index (<25 kg/m^2), (7) normotensive, (8) no metabolic syndrome, and (9) duration of diabetes of <10 years.

Table 5
Unadjusted and Adjusted Odds Ratio for the Association of Diabetes and Overweight/Obesity With SARS-CoV-2 Infection

Parameter	Seroprevalence	Unadjusted OR (95% CI)	Model 1[a] adjusted OR (95% CI)	Model 2[b] adjusted OR (95% CI)	Model 3[c] adjusted OR (95% CI)	Model 4[d] adjusted OR (95% CI)
Normal BMI and no diabetes (reference)	49/126 (38.9%)	Reference	Reference	Reference	Reference	Reference
Overweight/obese + no diabetes	101/208 (48.6%)	1.48 (0.95-2.33)	1.48 (0.95-2.33)	1.48 (0.94-2.32)	1.53 (0.97-2.40)	1.52 (0.96-2.38)
P value	…	.086	.086	.091	.066	.072
Normal BMI + diabetes	80/154 (52.0%)	1.70 (1.05-2.74)	1.77 (1.08-2.88)	1.58 (0.97-2.56)	1.80 (1.11-2.92)	1.69 (1.03-2.78)
P value	…	.030	.023	.065	0.018	0.039
Overweight/obese + diabetes	94/155 (60.7%)	2.42 (1.50-3.92)	2.59 (1.54-4.37)	2.31 (1.42-3.75)	2.66 (1.61-4.39)	2.63 (1.54-4.47)
P value	…	<.001	<.001	.001	<0001	<.001

Abbreviations: BMI = body mass index; OR = odds ratio.
[a] Model 1: adjusted for age and sex.
[b] Model 2: adjusted for education and occupation.
[c] Model 3: adjusted for hypertension.
[d] Model 4: adjusted for covariates in models 1 and 2.

with diabetes.[34] Compared with the existing studies that focused on patients with moderate-to-severe disease, we included individuals with asymptomatic or mild disease; thus, our study adds useful information to the existing literature on the subject of humoral immune response in diabetes.

We found a significant association between the presence of overweight/obesity and SARS-CoV-2 infection, both in the entire cohort of study participants and in the subset of individuals with diabetes. Further, the magnitude of association between SARS-CoV-2 and diabetes was stronger in individuals with coexistent overweight/obesity than in those without. These findings are in agreement with the existing literature, which suggests that obesity is associated with an increased risk of respiratory tract infections, both upper (adjusted OR, 1.55 [95% CI, 1.22-1.96]) and lower (adjusted OR, 2.02 [95% CI, 1.36-3.00]).[35] In the context of COVID-19, obesity is associated with an increased risk of severe disease (OR, 2.09 [95% CI, 1.67-2.62]) and mortality (OR, 1.49 [95% CI, 1.20-1.85]) [36].[36] The possible factors accounting for increased susceptibility and disease severity in obesity include the following: (1) immune dysregulation and chronic inflammation; (2) respiratory compromise and impaired pulmonary perfusion due to excess body fat; and (3) the presence of other comorbidities such as diabetes, hypertension, and cardiovascular disease.[37,38]

Apart from diabetes and overweight/obesity, low education level was associated with an increased risk of SARS-CoV-2 infection. Previous studies have shown differences in risk perception, knowledge, attitude, and protective behavior for COVID-19 according to education level, with lesser scores among those with low education level.[39,40] Further, a recent study from Peru highlighted an association between low education level and COVID-19 mortality, which was present across all age groups (<50 years, 50-70 years, and >70 years).[41] Social and economic inequality and the presence of adverse health behaviors were cited as the major reasons for this association. Our study findings further advance this proposition. Not only does low education status impact COVID-19 outcomes but it also increases susceptibility for acquiring the infection, especially in association with other factors such as diabetes and elevated BMI. Adverse behavioral and socioeconomic factors associated with low education status that promote a risk-taking attitude may account for this observation.

The major strengths of our study are its novelty and a large sample size. We included participants with both major types of diabetes, T1DM and T2DM, to evaluate any differential effect of diabetes type on disease susceptibility. In the study control group, diabetes was excluded using a combination of tests, that is, oral glucose tolerance test and HbA1c level measurements, and not based on history alone. A majority of participants had mild or asymptomatic infection, a disease pattern that corresponds to the one reported in the general population. We measured covariates for all participants and accounted for them in the adjusted analysis. We acknowledge certain limitations. Since the study participants were recruited from a tertiary care hospital, they may be different from the general population in certain aspects; this may limit the generalizability of our study findings. A proportion of participants in the control group had prior gestational diabetes. These women were exposed to hyperglycemia in the past and remain at high risk of future diabetes; however, they did not meet the criteria for diabetes in the present assessment. Rapid decay of antibody response and lower seroprevalence rates have been reported in patients with mild/asymptomatic infection.[42,43] The seroprevalence data reported in our study could, therefore, be an underestimate. However, since the proportion of participants with mild/asymptomatic disease was comparable between cases and controls, there are no implications for the principal findings of the study. Our

study suggests an association between diabetes and the risk of acquiring SARS-CoV-2 infection; however, due to its cross-sectional design, we cannot comment on causality. Future studies should evaluate the mechanisms for this association and inform strategies to mitigate the increased risk.

Conclusions

SARS-CoV-2 seropositivity, assessed before the onset of the national vaccination program and, therefore, the prevalence of infection, either asymptomatic or symptomatic, was significantly higher in participants with T1DM and T2DM than in healthy controls. Diabetes was associated with an increased risk of SARS-CoV-2 infection, and the magnitude of association further increased in participants with coexisting overweight/obesity. The antibody response did not differ between seropositive participants with and without diabetes. These findings point toward an increased SARS-CoV-2 susceptibility for patients with diabetes, in general, without any differential effect of the diabetes type.

Acknowledgment

We thank the study participants for generously donating their time and information. Moreover, we thank Vineeta Garg, BSc, Uday Shankar, MSW, and Reshmi Chhokar, BDS for their help in collecting study data and acknowledge the departmental laboratory staff for performing analysis of study samples.

Author Contributions

A.G., Y.G., and N.T. conceptualized this research and were involved in execution, analysis, manuscript preparation, and final approval of publication of this work. M.K. helped with statistical part and initial planning and final analysis of data, preparation of manuscript, and final approval of publication of this work. P.A.P. and S.A. helped in providing inputs in planning, patient recruitment, manuscript editing, and final approval of publication of this work. N.T. is the guarantor of this work and has full access to the data.

Disclosure

The authors have no multiplicity of interest to disclose.

Data Availability

The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. World Health Organization coronavirus disease (COVID-19) dashboard. Accessed June 19, 2021. https://covid19.who.int/.
2. International Diabetes Federation. IDF diabetes atlas, ninth edition. Accessed June 19, 2021. www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf.
3. Singh AK, Gillies CL, Singh R, et al. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2020;22(10):1915–1924.
4. de Almeida-Pititto B, Dualib PM, Zajdenverg L, et al. Severity and mortality of COVID 19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. *Diabetol Metab Syndr*. 2020;12:75.
5. Pranata R, Henrina J, Raffaello WM, Lawrensia S, Huang I. Diabetes and COVID-19: the past, the present, and the future. *Metabolism*. 2021;121:154814.
6. Lecube A, Pachón G, Petriz J, Hernández C, Simó R. Phagocytic activity is impaired in type 2 diabetes mellitus and increases after metabolic improvement. *PLoS One*. 2011;6(8), e23366.
7. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab*. 2020;318(5):E736–E741.
8. Rao S, Lau A, So HC. Exploring diseases/traits and blood proteins causally related to expression of ACE2, the putative receptor of SARS-CoV-2: a Mendelian randomization analysis highlights tentative relevance of diabetes-related traits. *Diabetes Care*. 2020;43(7):1416–1426.
9. Codo AC, Davanzo GG, Monteiro LB, et al. Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1α/glycolysis-dependent axis. *Cell Metab*. 2020;32(3):437–446.e5.
10. Kim JH, Park K, Lee SB, et al. Relationship between natural killer cell activity and glucose control in patients with type 2 diabetes and prediabetes. *J Diabetes Investig*. 2019;10(5):1223–1228.
11. Inbaraj LR, George CE, Chandrasingh S. Seroprevalence of COVID-19 infection in a rural district of South India: a population-based seroepidemiological study. *PLoS One*. 2021;16(3):e0249247.
12. Yadav R, Acharjee A, Salkar A, et al. Mumbai mayhem of COVID-19 pandemic reveals important factors that influence susceptibility to infection. *EClinicalMedicine*. 2021;35:100841.
13. Liang WH, Guan WJ, Li CC, et al. Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicentre) and outside Hubei (non-epicentre): a nationwide analysis of China. *Eur Respir J*. 2020;55(6):2000562.
14. Lian J, Jin X, Hao S, et al. Analysis of epidemiological and clinical features in older patients with coronavirus disease 2019 (COVID-19) outside Wuhan. *Clin Infect Dis*. 2020;71(15):740–747.
15. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934–943.
16. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):811–818.
17. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020;323(16):1574–1581.
18. Lampasona V, Secchi M, Scavini M, et al. Antibody response to multiple antigens of SARS-CoV-2 in patients with diabetes: an observational cohort study. *Diabetologia*. 2020;63(12):2548–2558.
19. CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019—United States, February 12 - March 28, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(13):382–386.
20. de Souza R, Mhatre S, Qayyumi B, et al. Clinical course and outcome of patients with COVID-19 in Mumbai City: an observational study. *BMJ Open*. 2021;11(5), e042943.
21. Kumar R, Bhattacharya B, Meena VP, et al. Characteristics and outcomes of 231 COVID-19 cases admitted at a tertiary facility in India: an observational cohort study. *J Family Med Prim Care*. 2020;9(12):6267–6272.
22. COVID-19 vaccines for seniors and 45-plus with comorbidities from March. Accessed June 19, 2021. https://www.thehindu.com/news/national/covid-19-vaccination-for-senior-citizens-from-march-1/article33922897.ece.
23. Goyal A, Gupta Y, Kalaivani M, et al. Long term (>1 year) postpartum glucose tolerance status among Indian women with history of gestational diabetes mellitus (GDM) diagnosed by IADPSG criteria. *Diabetes Res Clin Pract*. 2018;142:154–161.
24. Goyal A, Gupta Y, Kalaivani M, et al. Concordance of glycaemic and cardiometabolic traits between Indian women with history of gestational diabetes mellitus and their spouses: an opportunity to target the household. *Diabetologia*. 2019;62(8):1357–1365.
25. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43(suppl 1):S14–S31.
26. World Health Organization. Obesity and overweight. Accessed June 19, 2021. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
27. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560–2572.
28. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. Accessed June 19, 2021. http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf.
29. Murhekar MV, Bhatnagar T, Thangaraj JWV, et al. SARS-CoV-2 seroprevalence among the general population and healthcare workers in India, December 2020-January 2021. *Int J Infect Dis*. 2021;108:145–155.
30. Sharma N, Sharma P, Basu S, et al. The seroprevalence of severe acute respiratory syndrome coronavirus 2 in Delhi, India: a repeated population-based seroepidemiological study. *Trans R Soc Trop Med Hyg.* Published online August 2, 2021. https://doi.org/10.1093/trstmh/trab109
31. Babu NM. Sero survey shows 56% have antibodies. *The Hindu*; February 2, 2021. Accessed June 19, 2021. https://www.thehindu.com/news/cities/Delhi/sero-survey-shows-56-have-antibodies/article33722284.ece.
32. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239–1242.

33. Dispinseri S, Lampasona V, Secchi M, et al. Robust neutralizing antibodies to SARS-CoV-2 develop and persist in subjects with diabetes and COVID-19 pneumonia. *J Clin Endocrinol Metab*. 2021;106(5):1472–1481.
34. Schillie SF, Spradling PR, Murphy TV. Immune response of hepatitis B vaccine among persons with diabetes: a systematic review of the literature. *Diabetes Care*. 2012;35(12):2690–2697.
35. Maccioni L, Weber S, Elgizouli M, et al. Obesity and risk of respiratory tract infections: results of an infection-diary based cohort study. *BMC Public Health*. 2018;18(1):271.
36. Huang Y, Lu Y, Huang YM, et al. Obesity in patients with COVID-19: a systematic review and meta-analysis. *Metabolism*. 2020;113:154378.
37. Kwok S, Adam S, Ho JH, et al. Obesity: a critical risk factor in the COVID-19 pandemic. *Clin Obes*. 2020;10(6):e12403.
38. Goyal A, Gupta Y, Kalaivani M, Bhatla N, Tandon N. Impact of SARS-CoV-2 on progression of glycemic and cardiometabolic variables and changes in insulin indices: a longitudinal study. *Diabetes Ther*. 2021;12(11):3011–3023.
39. Rattay P, Michalski N, Domanska OM, et al. Differences in risk perception, knowledge and protective behaviour regarding COVID-19 by education level among women and men in Germany. Results from the COVID-19 Snapshot Monitoring (COSMO) study. *PLoS One*. 2021;16(5):e0251694.
40. Honarvar B, Lankarani KB, Kharmandar A, et al. Knowledge, attitudes, risk perceptions, and practices of adults toward COVID-19: a population and field-based study from Iran. *Int J Public Health*. 2020;65(6):731–739.
41. Concepción-Zavaleta MJ, Coronado-Arroyo JC, Zavaleta-Gutiérrez FE, Concepción-Urteaga LA. Does level of education influence mortality of SARS-CoV-2 in a developing country? *Int J Epidemiol*. 2021;49(6):2091–2093.
42. Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al. Rapid decay of anti-SARS-CoV-2 antibodies in persons with mild covid-19. *N Engl J Med*. 2020;383(11):1085–1087.
43. Thiruvengadam R, Chattopadhyay S, Mehdi F, et al. Longitudinal serology of SARS- CoV-2-infected individuals in India: a prospective cohort study. *Am J Trop Med Hyg*. 2021;105(1):66–72.