COVID-19 Hospitalization in Adults with Type 1 Diabetes: Results from the T1D Exchange Multi-Center Surveillance Study

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Abstract

Context: Diabetes mellitus is associated with increased COVID-19 morbidity and mortality, but there is little data focusing on outcomes in people with type 1 diabetes.

Objective: The objective of this study was to analyze characteristics of adults with type 1 diabetes for associations with COVID-19 hospitalization.

Design: An observational multi-site cross-sectional study was performed. Diabetes providers answered a 33-item questionnaire regarding demographics, symptoms, and diabetes- and COVID-19-related care and outcomes. Descriptive statistics were used to describe the study population, and multivariate logistic regression models were used to analyze the relationship between HbA1c, age, and comorbidities and hospitalization.

Setting: Cases were submitted from 52 US sites between March and August 2020.

Patients or Other Participants: Adults over the age of 19 with type 1 diabetes and confirmed COVID-19 infection were included.

Interventions: None

Main Outcome Measures: Hospitalization for COVID-19 infection

Results: A total of 113 cases were analyzed. Fifty-eight patients were hospitalized, and five patients died. Patients who were hospitalized were more likely to be older, to identify as non-Hispanic Black, to use public insurance, or to have hypertension, and less likely to use continuous glucose monitoring or insulin pumps. Median HbA1c was 8.6% (70 mmol/mol) and was positively associated with hospitalization (OR 1.42, 95% CI 1.18-1.76), which persisted after adjustment for age, sex, race, and obesity.

Conclusions: Baseline glycemic control and access to care are important modifiable risk factors which need to be addressed to optimize care of people with type 1 diabetes during the worldwide COVID-19 pandemic.

Keywords: Type 1 diabetes, Adult, Hospitalization, COVID-19

Introduction

Pre-existing diabetes has been found to be a risk factor for COVID-19 associated morbidity and mortality. The odds of a fatal outcome from COVID-19 have been reported to be 0.5-3.5 times higher in patients with diabetes compared to those who do not have diabetes (1-3).

In addition to the increased risk of mortality, there are higher reported rates of fatigue, dyspnea, lymphopenia, increased inflammatory markers, decreased kidney function, low oxygen saturation, steroid use, acute respiratory distress syndrome, need for mechanical ventilation, and longer length of stay in patients with diabetes compared to those without diabetes (1; 2). In patients with diabetes hospitalized for COVID-19, there are high rates of hyperglycemia and diabetic ketoacidosis (4; 5). Hyperglycemia at the time of admission and throughout hospitalization is associated with less optimal patient outcomes (1; 2; 6). An inpatient blood glucose range of 70-180 mg/dL was associated with a mortality hazard ratio of 0.14 compared to glucose values >180 mg/dL for patients 18-75 years old with type 2 diabetes (1). The better controlled group had a lower median HbA1c (7.3% vs 8.1%; 56 vs 65 mmol/mol) and less lymphopenia, acute kidney injury, low oxygen saturation, steroid use, and ventilation (1). The emerging literature for diabetes outcomes in COVID-19 infection is similar to data from the SARS and MERS pandemics (1).

The majority of the literature analyzes outcomes in patients with any diabetes or type 2 diabetes, but data about patients with type 1 diabetes are limited. An analysis of healthcare claims in England specifically looking at type 1 diabetes found that, when adjusted for cardiovascular disease, age, sex, deprivation, ethnicity, and geographical region, there was a 2.86 times higher odds (CI (2.58–3.18) of in-hospital death with COVID-19 for those with type 1 diabetes compared to those without known diabetes (odds without cardiovascular disease adjustment 3.51, CI 3.16-3.90) (3). Of COVID-19-related deaths in patients with type 1 diabetes, there was a hazard ratio of 2.23 (CI 1.5-3.3) of having an HbA1c of >10% (>86 mmol/mol) compared to HbA1C of 6.5-7% (48-53 mmol/mol) (7).

Other risks for hospitalization and mortality in the general population with COVID-19 include increasing age, male sex, racial and ethnic minorities, elevated body mass index, heart failure, and cardiovascular disease. The strongest predictors of critical illness in the general COVID-19 positive population are low oxygen saturation, elevated inflammatory markers, and age >64 years (8).

The T1D Exchange Quality Improvement Collaborative was established to improve care delivery for people with type 1 diabetes (9) and recently initiated a COVID-19 surveillance study to gather multi-site data. We previously described 33 COVID-19 positive patients with mean age 24.8 years (range 7-79) and median HbA1C of 8.5% (69 mmol/mol). The most prevalent presenting symptom in this smaller cohort was high blood glucose (48.5%). The most prevalent comorbidity was obesity (39.4%). The most prevalent adverse outcome was diabetic ketoacidosis (45.5%) (10).

The primary objectives of this manuscript were to describe a larger adult population of patients with type 1 diabetes and COVID-19 and to determine if epidemiologic and patient characteristics were associated with increased odds for hospitalization.

Materials and Methods

A cross-sectional study was performed at 52 sites across 22 US states, the list of sites is available as a supplemental table (11). The study was reviewed by a central review board (Western Institutional Review Board) and approved as exempt. The T1D Exchange Quality Improvement Collaborative sponsored and coordinated data collection and analysis.

Diabetes providers performed retrospective chart review of patients with confirmed COVID-19 from March 1, 2020 – August 22, 2020. Providers queried their local databases per local procedures to identify cases. Deidentified data was collected via a 33-item questionnaire using Qualtrics software, version XM (12). Patients with type 1 diabetes who had confirmed COVID-19 infection were included. Patients aged 19 years and older were included in this analysis. The age cutoff was chosen to be in line with the most common state reporting practices since 36 of 49 reporting states use this age cutoff for delineating pediatric from adult cases (13). Patients were classified as COVID-19 positive if they had tested positive for COVID-19 through a molecular test. Information on demographic characteristics, diabetes history and management, COVID-19 symptoms and management, and comorbidities was included. Each submitted case was reviewed by central researchers for potential errors in data entry or incomplete information, and random validation of data was performed to ensure quality assurance.

The primary outcome of interest for this manuscript was hospitalization. This was defined as a binary outcome, with patients reported to have been hospitalized or admitted to an intensive care unit being grouped under hospitalized patients, whereas patients who received at home care, or were seen at clinic or emergency department, being grouped under home care. Patient symptoms, comorbidities, and outcomes of each patient were analyzed as categorical variables. Insurance types were classified as public, private, uninsured, or unknown.

Mean (standard deviation) or median (interquartile range) are reported for continuous variables. Categorical data were represented as the percentage of patients. P-values were calculated using fisher's exact or chi-square tests to examine the associations between the categorical variables. Logistic regression analysis was performed and odds ratios reported to look at the association between HbA1c and hospitalization status. Models were adjusted for age, sex, race, and obesity. HbA1c variable was natural log transformed for analysis. All analyses were performed using Python 3 and R statistical software, version 3.6 (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical computing, Vienna, Austria, 2020, https://www.R-project.org).

Results

A total of 113 patients were identified for analysis, with a mean age of 39.9 years (range 20-80), 58% female, and median HbA1c of 8.6% (IQR 5.4-11.8) (70, IQR 36-105 mmol/mol). Demographics, diabetes history, symptoms and outcomes are summarized in Table 1.

Fifty-eight (51%) patients were hospitalized, and 55 (49%) were managed at home or in an ambulatory setting (Table 1). Hospitalized patients were older (hospitalized: 44.9 years vs non-hospitalized 34.6 years, p<0.001), and were more likely to identify as non-Hispanic Black (40% vs 13%, p=0.001), to have public insurance (78% vs 18%, p<0.001), and to have hypertension (57% vs 18%, p<0.001); and were less likely to use an insulin pump (12% vs 53%, p<0.001) or a continuous glucose monitor (17% vs 73%, p<0.001). The median HbA1c was higher for hospitalized patients (9.0% vs 7.6%, 75 vs 60 mmol/mol, p<0.001). There was no difference in ACEi, ARB, or statin use (ACEi 18% vs 13%, p=0.8, ARB 40% vs 33%, p=0.43, statin 41% vs 40%, p=0.9).

The odds of being hospitalized increased with higher A1c values (OR 1.42, 95% CI 1.18-1.76, p<0.01). This association persisted when adjusted for age, sex, race, and obesity (Table 2). Hospitalization was also more likely with increasing age (OR 1.05, 95% CI 1.02-1.06, p<0.01), minority race or ethnicity (OR 3.63, CI 1.42-9.70, p<0.01), and cardiovascular disease (including hypertension) (OR 3.36, CI 1.16-10.28, p<0.01. Chronic kidney disease and sex were not significant predictors of hospitalization when adjusted for age, race, obesity, and HbA1c.

Of the 58 hospitalized patients, 26 were admitted to an intensive care unit and five men died during hospitalization for COVID-19. Characteristics of the five men who died were as follows: (1) A 79-year-old Hispanic man with type 1 diabetes for over 20 years, hypertension, and HbA1c of 9.3% (78 mmol/mol), (2) A 61 year old Hispanic man with type 1 diabetes for over 20 years, on chronic hemodialysis, and HbA1c of 8.6% (70 mmol/mol) who was admitted with diabetic ketoacidosis and died from respiratory failure, (3) A 56-year-old man of unknown race with type 1 diabetes for over 10 years, HbA1c of 14% (130 mmol/mol), and a history of hypertension and stroke who died of acute respiratory distress syndrome, (4) A 36 year old Hispanic male with type 1 diabetes for over 20 years with HbA1C of 10.6%, hypertension, chronic hemodialysis, peripheral vascular disease, and congestive heart failure, and (5) A 34 year old non-Hispanic White man with type 1 diabetes for over 20 years with HbA1c of 7.8%, hypertension, obesity, and atrial fibrillation who was admitted for surgical management of a traumatic fracture, developed respiratory failure from COVID-19 complicated by diabetic ketoacidosis after steroid treatment, and died from acute respiratory distress syndrome.

Discussion

Patients with type 1 diabetes and COVID-19 were more likely to be hospitalized if they were older, identified as non-Hispanic Black, had public insurance, had a higher HbA1c, or had hypertension. Risk factors identified in our analysis are similar to previously published literature on COVID-19 hospitalization in the general population in terms of sociodemographics and comorbidities. In contrast to previous literature, there was no difference in likelihood of hospitalization with obesity. It is unclear if our lack of finding an association between obesity and hospitalization has to do with lower overall obesity rates in the type 1 diabetes populations compared to type 2 diabetes, or if there is some independent mechanism related to morbidity and mortality that is not captured in this study's cohort. We also found no difference in gender for hospitalization rates, which has been previously reported, however, all five of the mortality cases were men.

Lower rates of continuous glucose monitoring and insulin pump use, and higher public insurance in hospitalized patients are all likely interconnected with access to diabetes care. Consistent with emerging literature, higher HbA1c was associated with higher likelihood of hospitalization.

Diabetic ketoacidosis was likely a major driver of hospitalization since 47% of hospitalized patients had diabetic ketoacidosis. The underlying reason for increased rates of diabetic ketoacidosis with COVID-19 infections is still unclear, though it is well known that viral illnesses may precipitate diabetic ketoacidosis events. Stress hyperglycemia is likely a major contributing factor. Literature related to type 2 diabetes during the SARS pandemic also suggests that there may be a direct effect of the virus on beta cells in patients with type 2 diabetes or no preexisting diabetes (14); however, for people with long duration of type 1 diabetes with minimal if any residual pancreatic function, this is unlikely to be a major contributing factor. There may also be other causes of increased acidosis since there was also a high mean anion gap reported for COVID-19 patients without hyperglycemia or pre-existing diabetes (2).

The majority of literature regarding diabetes and COVID-19 morbidity and mortality is reported without a breakdown of outcomes specifically for type 1 versus type 2 diabetes. The assumption that these diseases would confer the same risk of infection and death, however, is not established. Barron et al found a higher adjusted odds ratio for in-hospital COVID-19-related death in people with type 1 diabetes (2.86) compared to type 2 diabetes (1.80). Some of the physiology which may predispose people with diabetes to increased risk of COVID-19 complications may be shared such as alterations to the immune system and susceptibility to inflammation (15). Our analysis and others have found age and race/ethnicity to be a risk factor for poorer outcomes, and the population with type 2 diabetes is overall older and includes higher proportions of minority races and ethnicities. Our analysis did not find a strong influence of obesity which is closely associated with type 2 diabetes. The higher odds ratio for in-hospital death in people with type 1 diabetes found by Barron et al could be affected by a higher risk diabetic ketoacidosis or severe hypoglycemia. There are also likely differences in rates of other comorbidities such as cardiovascular disease, potential

differences in physiology such as ACE2 expression and risk of thromboembolism, and social differences in access to healthcare and likelihood of preventative self-isolation. Further elucidation of the pathophysiology of COVID-19 complications and analysis of diabetes by type whenever possible are needed to specifically evaluate how diabetes and control of blood sugars affects risk for infection, risk of hospitalization, and risk of morbidity and mortality.

We present the most detailed description of cases of COVID-19 infection in adults with type 1 diabetes in the United States across 52 sites in 22 US states. Our dataset included a diverse population across geography, race and ethnicity, insurance type, and diabetes care based on HbA1c and use of continuous glucose monitoring and insulin pumps.

Strengths of this study are that the data set presents a diverse group of people with type 1 diabetes specifically, with more detail on medical history and diabetes care than previously published. Limitations in our analysis include selection bias, which could increase the proportion of hospitalized patients included, lack of testing capacity during the early months of the COVID-19 pandemic which may have limited the number of reported infections, limited ability to capture asymptomatic infection, missing data, limited data on diabetes control during infection and/or hospitalization, and limited data on COVID-19 management such as steroid use.

Type 1 diabetes increases the risk of morbidity and mortality with COVID-19 infection. People with type 1 diabetes and other comorbid conditions were more likely to be hospitalized with COVID-19. Baseline glycemic control and markers of access to care are important modifiable risk factors which need to be addressed preemptively to optimize care of patients with type 1 diabetes during the worldwide COVID-19 pandemic. Further evaluation of the impact of modifiable risk factors to reduce severe illness is needed.

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Tables

Table 1: Demographics and characteristics of hospitalized and non-hospitalized patients with confirmed COVID-19

	Total (N=113)	Hospitalized (N=58)	Non-Hospitalized (N=55)	P Value
Mean Age (SD)	39.9 (16.4)	44.9 (17.1)	34.6 (13.9)	<0.001
Age Category, years, N (%)				
20 to 30	42 (37)	15 (26)	27 (49)	0.01
31 to 40	19 (17)	8 (14)	11 (20)	0.45
41 to 50	18 (16)	8 (14)	10 (18)	0.61
51 to 60	15 (13)	12 (21)	3 (5)	0.02
61+	19 (17)	15 (26)	4 (7)	0.01
Sex (Female)	58 (51)	26 (45)	32 (58)	0.18
Race/Ethnicity				
NH White	54 (48)	17 (29)	37 (67)	<0.001
NH Black	30 (27)	23 (40)	7 (13)	0.001
Hispanic	21 (19)	14 (24)	7 (13)	0.14
Other	8 (7)	4 (7)	4 (7)	1
Insurance Type				
Public	55 (49)	45 (78)	10 (18)	<0.001
Private	54 (48)	10 (17)	44 (80)	<0.001
Uninsured	4 (4)	3 (5)	1 (2)	0.61
HbA1c Median (IQR)	8.6 (3.2)	9 (3.5)	7.6 (2.3)	<0.001
HbA1c Category				
Less than 7%	23 (20)	4 (7)	19 (35)	<0.001
7 – 9%	49 (43)	26 (45)	23 (42)	0.84
More than 9%	41 (36)	28 (48)	12 (24)	0.01
Duration of T1D				
New onset	2 (2)	2 (3)	0 (0)	0.49
Less than 1 year	1 (1)	0 (0)	1 (2)	0.48
1- 5 years	7 (6)	2 (3)	5 (9)	0.26
6-10 years	12 (11)	9 (16)	3 (5)	0.12
11-20 years	43 (38)	18 (31)	25 (45)	0.12
More than 20 years	48 (42)	27 (47)	21 (38)	0.44
CGM Use				
Yes	50 (44)	10 (17)	40 (73)	<0.001
Insulin Pump Use				
Yes	36 (32)	7 (12)	29 (53)	<0.001
Most common symptoms*				
High Blood Sugar	34 (30)	25 (43)	9 (16)	0.002
Elevated Temperature	56 (50)	30 (52)	26 (47)	0.7
Dry Cough	58 (51)	31 (53)	27 (49)	0.7
Nausea	34 (30)	26 (45)	8 (15)	<0.001
Excess Fatigue	43 (38)	18 (31)	25 (45)	0.12

Body/Head aches	38 (34)	12 (21)	26 (47)	0.004
Vomiting	23 (20)	23 (40)	0 (0)	<0.001
Shortness of breath	38 (34)	29 (50)	9 (16)	<0.001
Comorbidity present				
Yes	87 (77)	54 (93)	33 (60)	<0.001
Most Prevalent Comorbidities				
Obesity	18 (16)	10 (17)	8 (15)	0.79
Hypertension	43 (38)	33 (57)	10 (18)	<0.001
Cardiovascular Disease	23 (20)	14 (24)	9 (16)	0.35
Asthma	9 (8)	6 (10)	3 (5)	0.49
Chronic Kidney Disease	30 (27)	22 (38)	8 (15)	0.005
Most Prevalent Medications				
ACE Inhibitors	17 (15)	10 (18)	7 (13)	0.8
ARB	40 (35)	22 (40)	18 (33)	0.43
Beta blockers	17 (15)	11 (19)	6 (11)	0.09
Statins	46 (40)	24 (41)	22 (40)	0.9
Antidepressants	13 (12)	9 (16)	4 (7)	0.1
Adverse Outcome				
Death	5 (4)	5 (9)	0 (0)	0.05
DKA	27 (24)	27 (47)	0 (0)	<0.001
Severe Hypoglycemia	6 (6)	5 (9)	1 (2)	0.2
Tracheal Intubation	6 (6)	6 (10)	0 (0)	0.11
None	68 (60)	15 (26)	54 (98)	<0.001

Abbreviations: SD=standard deviation, IQR=interquartile range, T1D=type 1 diabetes, CGM=continuous glucose monitoring, DKA=diabetic ketoacidosis. *Subjects could report more than one symptom.

Table 2: Odds ratio for hospitalization in confirmed COVID-19 patients (N=113)

	Unadjusted	Fully Adjusted
HbA1c	1.42 (1.18, 1.76) *	1.43 (1.16, 1.82) *
Age	-	1.05 (1.02, 1.08) *
Gender	-	1.05 (0.90, 1.98)
Race	-	3.63 (1.42, 9.70) *
CVD	-	3.36 (1.16, 10.28) *
CKD	-	2.75 (0.91, 8.74)

Fully adjusted for Age (as a continuous variable), Gender (Male vs Female), Race (Minority – NH Black, Hispanic, Other vs. NH White), Obesity (Yes vs No) and HbA1c (as a continuous variable), CVD – Cardiovascular disease including hypertension.

*P Value less than 0.01