



Research Article

Real-World Data Analysis During the First-Wave Coronavirus Pandemic from a Diabetic Unit in Central North Italy: Old Oral Hypoglycaemic Agents and Insulin Show to be Associated with Higher Hospital Admissions and Total Mortality and Glifozines Seem to Protect from Total Mortality in Covid-19+ T2DM Patients

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Abstract

Aim: From the start of the SARS-Cov2 pandemic in Wuhan in December 2019 the global mean mortality rate is 2.8% (range 2.3 ÷ 15.2%). We asked if type 1 (T1DM) and type 2 (T2DM) diabetic people - during the first wave pandemic period - could be at different risk of i) acquiring SARS-CoV2 infection; ii) hospitalization; iii) dying, and iv) if there was a link between the course of Covid-19 infection and the type of antidiabetic drugs. **Methods:** We analysed three outcomes from laboratory and hospital registries: #1) positivity to a SARSCov2-PCR nasal swab test; #2) hospital admission due to COVID-19; #3) death for any cause in covid+ patients. **Results:** Cumulative outcomes by 1,426 T1DM and 25,776 T2DM patients showed no difference in the positivity of a SARS-Cov2 nasal swab (0.8 vs 1.0% T1DM vs T2DM, $P > 0.05$) whereas we found a significant difference both in the rates of in-hospital admission (0.2 vs 0.7% T1DM vs T2DM, $P < 0.05$) and mortality for any cause (0.9 vs 2.5% T1DM vs T2DM, $P < 0.05$). In T2DM hospitalization resulted significantly associated with male sex, older age and to be on old antidiabetic drugs; total mortality was associated with male sex, age and insulin therapy, and it was inversely associated with glifozines. **Conclusions:** The present overlap of both Covid-19 and the diabetic pandemic could be a challenge but also an opportunity to improve the care of diabetes and to change clinical practice.

Keywords: Diabetes mellitus; Covid-19; Clinical pharmacology; Pandemic; Mortality; Hospitalization; Glifozines; Insulin; Antidiabetic drugs

Introduction

Coronavirus disease 2019, caused by a novel acute respiratory syndrome coronavirus (SARSCoV2), was declared to be a pandemic by the World Health Organisation on 11 March 2020 and had aroused worldwide public concern. From the start of the pandemic in Wuhan in December 2019 to date, 22 April 2021, the virus has infected 137,603,448 people with 2,876,691 deaths worldwide [1]. The global mean mortality rate is 2.8% (median age of 75 years), but the value ranges from 2.3% to 15.2%, depending on patient populations, diagnostic strategies and other factors. The need for Intensive Care Unit (ICU) admission is around 20% [2]. Several clinical conditions are described as associated with a higher risk for severe complications and death in Covid-19 infected patients, i.e., cardiovascular disease, diabetes and Chronic Kidney Disease (CKD). The fatality rate was 10.5% in persons with cardiovascular disease, 7.3% in diabetes, 6% in hypertension according to a population-based retrospective study in China [3]. A meta-analysis including 1,527 patients in Wuhan reported that hypertension, CVD and diabetes were the most prevalent disease observed in the patient with severe COVID-19 complications (17.1%, 16.4 and 9.7% respectively) [4].

Preliminary data from a sample of 355 patients who died of Covid-19 in Italy, showed a prevalence of diabetes of 35.5% [5]. Notably, more than 65% of diabetic patients were over 65 years of age, who also had a high age-specific risk of disease. Noteworthy, few data are available about the two main types of diabetes, i.e., autoimmune type 1 (T1DM) and type 2 (T2DM) diabetes mellitus.

Aim

As a result of these observations, many pertinent questions arose

- i) Did T1DM autoimmune and T2DM people show to be at different risks of acquiring SARS-CoV2 infection?
- ii) Did T1DM and T2DM people show to be at different risk to be hospitalized due to SARS-CoV2 infection?
- iii) Did T1DM and T2DM people show to be at different risks of dying during the first wave pandemic period?
- iv) Is there a link between the course of SARS-COV2 infection and the type of antidiabetic drugs the patients assumed?

Such questions have a potential interest to change clinical practice during the ongoing pandemic period too.

To answer these questions, we revised clinical outcomes in the study period January-September 2020 accounting for gender, age, type of diabetes and ongoing hypoglycaemic drugs (insulin,

dipeptidyl-peptidase IV inhibitors [DPP4i], sodium-glucose-cotransporter 2 inhibitors [SGLT2i], Glucagon-like peptide-1 receptor agonists [GLP-1 RAs], others hypoglycaemic agents [OHA]).

We have analysed the following three outcomes:

- #1) positivity to a SARS-Cov2-PCR nasal swab test
- #2)-hospital admission due to COVID-19
- #3) death for any cause in covid+ patients.

Materials and Methods

We extracted the study outcomes from the unique certified laboratory as to the positivity to a SARS-Cov2-PCR nasal swab test; in the patients covid-19 positive we analysed DRGs hospital database as to hospital admission due to COVID-19 and in-hospital mortality and from death registry for out-of-hospital mortality. T1DM and T2DM patients have given their written informed consent to Institutional data analysis of their clinical files for epidemiological and/or surveillance purposes.

To differentiate the type of diabetes (T1DM vs T2DM) we matched these data with those from the Diabetes institutional registry of the NHS Local Health Unit. We have collected all the T1DM and T2DM patients followed by the Diabetes Unit in the study period January-September 2020; we have categorized these patients regarding gender, age, type of diabetes and ongoing hypoglycaemic drugs (DPP4i, SGLT2i, GLP-1 RAs, OHA); OHA included sulphonylureas, glinides, pioglitazone, acarbose and metformin alone. We did not analyse separately metformin alone because in our current practice of a diabetes specialist second level care network we prescribe metformin at diagnosis as default due to population basic characteristics; furthermore, because of national reimbursement rules in our diabetologists network, we take care of T2DM with newer antidiabetic drugs, namely DPP4i, SGLT2i, GLP1-RAs and insulin for complicated disease both in monotherapy and in association with metformin or insulin or others.

Descriptive frequencies of patients' characteristics were calculated and expressed as number and percentage for categorical and dichotomous or mean (\pm std. dev.) for continuous variables.

We explored the association between the three study outcomes as independent variables and the study variables using multivariate logistic regression and expressed as Odds Ratios (OR) adjusted for age, sex and antidiabetic drugs. The significance of the P-value was < 0.05 .

Results

We studied 1,426 T1DM and 25,776 T2DM patients in the

first-wave pandemic (Jan-Sept 2020). Their characteristics and cumulative outcomes by type of diabetes are shown in table 1. Mean age resulted insignificant difference between the two groups T1DM vs T2DM of about two decades.

Cumulative study outcomes' frequencies showed no difference in the positivity of a SARS-Cov2 nasal swab (0.8 vs 1.0% T1DM vs T2DM, P > 0.05). We found a significant difference both in the rates of in-hospital admission (0.2 vs 0.7% T1DM vs T2DM, P < 0.05) and mortality for any cause (0.9 vs 2.5% T1DM vs T2DM, P < 0.05) in Covid+ patients (Table 1).

	T1DM (N. 1,426)		T2DM (N. 25,776)		P-value
	N.	%	N.	%	
Sex					
Female	614	43%	10751	42%	N.S.
Male	812	57%	15025	58%	N.S.
Age (mean ± std. dev.)	49.4 ± 16.6		69.0 ± 12.8		< .0001
Hypoglycaemic Drugs*					
Insulin	1203	84%	5563	22%	< .0001
DPP4i	49	3%	4172	16%	< .0001
GLP1-RA	1	0%	625	2%	< .0001
SGLT2i	24	2%	1939	8%	< .0001
OHA**	278	19%	18580	72%	< .0001
Outcomes	T1DM (N. 1,426)		T2DM (N. 25,776)		P-value
	N.	%	N.	%	
#1. SARS-Cov2+***	11	0.8%	255	1.0%	N.S.
#2. Hospital admission for severe COVID-19	3	0.2%	173	0.7%	0.0346
#3. Mortality (any cause)	13	0.9%	644	2.5%	0.0001

Table 1: Patients' characteristics and cumulative outcomes in the study period (Jan-Sept 2020);N.S. Not Significant = P-value 0.05;

*Metformin was associated with all drugs and not considered alone;**Other hypoglycaemic agents: sulphonylureas, glinides, pioglitazone, acarbose and metformin alone;*** SARS-Cov2-PCR nasal swab molecular test positivity.

In multivariate logistic regression, no significant association was found with outcome #1 - positivity to a SARS-Cov2 nasal swab molecular test. As to the outcome #2 - hospital admission - in T1DM no significant association was found. Whereas in T2DM outcome #2 resulted significantly associated with male sex, older age and to be on OHA therapy. As to the outcome #3 - total mortality - in T1DM it was significantly associated only with older age. In T2DM the outcome # resulted significantly associated with male sex, older age and to be on insulin therapy; it was inversely associated with current treatment with SGLT2i (Table 2).

Outcome #1. SARS-Cov2+ PCR nasal swab molecular test	T1DM (N. 1,426)		T2DM (N. 25,776)	
	Adj OR	P-value	Adj OR	P-value
Sex (F vs M)	0.71	N.S.	0.94	N.S.
Age (mean ± std. dev.)	1.00	N.S.	1.00	N.S.
Insulin (Yes vs No)	1.30	N.S.	1.14	N.S.

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DPP4i (Yes vs No)	0.86	N.S.	1.10	N.S.
GLP1-RA (Yes vs No)	0.62	N.S.	1.23	N.S.
SGLT2i (Yes vs No)	491.03	N.S.	0.80	N.S.
OHA* (Yes vs No)	0.004	N.S.	1.09	N.S.
	T1DM (N. 1,426)		T2DM (N. 25,776)	
Outcome #2. Hospital admission for severe COVID-19	Adj OR	P-value	Adj OR	P-value
Sex (F vs M)	0.83	N.S.	0.79	0.0045
Age (mean ± std. dev.)	1.00	N.S.	1.02	0.0009
Insulin (Yes vs No)	150.8	N.S.	1.13	N.S.
DPP4i (Yes vs No)	1.09	N.S.	1.13	N.S.
GLP1-RA (Yes vs No)	0.81	N.S.	1.16	N.S.
SGLT2i (Yes vs No)	0.91	N.S.	0.93	N.S.
OHA* (Yes vs No)	0.01	N.S.	1.27	0.0182
	T1DM (N. 1,426)		T2DM (N. 25,776)	
Outcome #3. Mortality (any cause)	Adj OR	P-value	Adj OR	P-value
Sex (F vs M)	0.95	N.S.	0.85	< .0001
Age (mean ± std. dev.)	1.10	< .0001	1.08	< .0001
Insulin (Yes vs No)	2.26	N.S.	1.65	< .0001
DPP4i (Yes vs No)	1.91	N.S.	1.09	N.S.
GLP1-RA (Yes vs No)	0.005	N.S.	0.67	N.S.
SGLT2i (Yes vs No)	0.004	N.S.	0.69	0.0036
OHA* (Yes vs No)	0.64	N.S.	0.97	N.S.
N.S. Not Significant = P-value 0.05; *Other hypoglycaemic agents: sulphonylureas, glinides, pioglitazone, acarbose and metformin alone.				

Table 2: Multivariate logistic regression in the study period (Jan-Sept 2020).

Discussion

Generally, individuals with diabetes are postulated to be at greater risk of respiratory tract infection compared to the healthy general population [13,14]; it has even been postulated that people with diabetes are more susceptible to Covid-19 and that SARS-Cov2 infection may also exacerbate hypoglycemia, inflammatory responses and diabetic complication, such as diabetic ketoacidosis, which increase the risk of being critically ill [7,8]. Fadini, et al. [12] found no significant increase in susceptibility to SARS-Cov2 infection in diabetic people but did find an increased risk of worse Covid-19 progression and outcomes. However, regardless of the type of diabetes, the severity of the disease differs according to

age, complications, and how well it is controlled [7]. We have no data about the susceptibility to SARS-Cov2 infection by the diabetic population in Modena, but we observe that the probability of testing positive in a SARS-Cov2-PCR nasal swab molecular test in the time range January-September 2020 was the same for T1DM and T2DM people. As depicted in Table 1, data collected from our database showed a lower number of SARS-Cov2 positive patients, hospitalization and death for any cause. Furthermore, neither gender nor age was related to an increased probability of testing positive in a nasal swab test. Interestingly, the probability of testing positive was not influenced by ongoing antidiabetic drugs. In particular, there was no evidence of protective effect by intake of DPP4 inhibitors. DPP4, originally known as cluster differentiation

26 (CD26), is a multifunctional soluble and cell-bound serine protease and plays a critical role in glucose homeostasis and inflammatory responses [9]. While the lung appeared to be the organ with the second-highest expression of DPP4/CD26 in rats, it was assumed that DPP4/CD26 system modulation may prevent the entry of the virus into the cells and stop the cytokine storm in the lung [11]. Nevertheless, current knowledge has not fully supported the beneficial effects of DPP4 inhibitors on patients with diabetes and Covid-19 [7-10].

We found significant differences between T1DM and T2DM about the risk of hospitalization due to Covid-19 (0.2% vs 0.7%) as well as the risk of death due to any cause (0.95% vs 2.5%). Interestingly, the mortality rates were lower than those reported above both in global mean mortality [2] and diabetes in China [3]. The differences between T1DM vs T2DM could be easily explained by the two decades significant difference in mean age (Table 1). Furthermore, in T2DM patients, we observed that older age and male sex are associated with higher adjusted OR for hospitalization. Noteworthy, in T2DM the ongoing therapy with drugs other than insulin, DPP4, GLP1-Ra and SGLT2, mainly sulphonylurea or glinides, resulted to be associated with a higher risk of hospitalization (Table 2).

The risk of death for any cause showed a different pattern between the two groups of patients, i.e., it was associated only with older age in T1DM while in T2DM patients it was associated with older age and male sex. The explanation about the sex-role differences in T1DM and T2DM is not included in the study design, however, we might suggest that a diagnosis of T1DM could account for the sex differences risk due to Covid-19 infection. To confirm our hypothesis further investigations are needed.

As to hypoglycaemic drugs in T2DM, the odds of death for any cause were associated with the use of insulin, which is associated with long-standing and more complicated diseases. Ongoing therapy with DPP4 inhibitors or GLP1-RAs does not appear to confer any protective effect on hospitalization or death among Covid-19 diabetic patients. Unexpectedly, home therapy with SGLT2 inhibitors (glifozines) was associated with a significantly lower death rate. SGLT2i are therapeutic drugs that promote renal excretion of glucose. As a potential adverse effect, they can produce volume contraction, risk of dehydration, and euglycemic diabetic ketoacidosis under particular pathophysiological conditions, such as acute inflammatory illness caused by SARS-cov2 infection. For these reasons, experts advise against the use of SGLT2i in diabetic and Covid-19 inpatient or during acute phase illness [2,14]. However, a lot of evidence showed the efficacy and metabolic and cardiovascular benefits of SGLT2i in the chronic care setting. Empagliflozin first showed a relative risk reduction of 14% in the primary outcome (composite of non-fatal myocardial

infarction or stroke, or death from cardiovascular causes), 38% in cardiovascular death, 35% in hospitalization for heart failure and 32% in all-cause mortality (15). Following empagliflozin, other glifozines shared such evidence on cardiovascular outcomes, both in diabetic and non-diabetic patients [16,17]. In particular, they reduced the rate of worsening heart failure and hospitalization for heart failure or cardiovascular and total mortality [18,19]. The same drugs collected great evidence about their nephroprotective effects, and they reduced the rate of the doubling of serum creatinine, or renal death or end-stage-renal-disease [20-22].

These data also highlight the importance of correctly approaching the diabetic patient, regarding phenotype [23], cardiovascular risk [28] and diabetic complications [24-26] and comorbidities [27]. As far as we can appropriately characterize the T2DM patient's profile, thus tailoring his treatment needs, we could be able to better prevent complications in chronic and in the acute setting of care to improve outcomes even during a severe acute illness such as Covid-19.

During the first wave of the pandemic: i) T1DM autoimmune and T2DM people showed the same risk of SARS-CoV2 infection; ii) T1DM showed a significantly lower risk than T2DM in hospitalization due to SARS-CoV2 infection iii) T1DM showed significantly lower mortality than T2DM; iv) antidiabetic drugs showed different influence on SarsCoV2 infection in T2DM traditional oral hypoglycaemic drugs and insulin were associated with higher hospital admissions and total mortality, whereas glifozines seemed to protect from total mortality in Covid-19+ and T2DM patients.

The low rate of SARS-CoV2 positive patients observed in our study might be related to 1) effective communication with diabetic patients to increase their awareness on the risk of SARS-CoV2 infection in the presence of diabetes, 2) a successful and innovative remote management of diabetic patients both scheduled and on-demand, and 3) careful sanctification and management of patients in the waiting areas to avoid interpersonal contact.

In Italy, reimbursement rules are under revision because the time has come to extend the prescription of innovative antidiabetic drugs to the totality of clinicians, mainly the general practitioners, to provide effective fair treatment with innovative drugs thus allowing the GPs to have an active role in the management of diabetic patients.

This new opportunity could be of great help either for clinicians to improve the management of treatment and for diabetic patients to improve their quality of life. The present overlap of both Covid-19 and diabetic ongoing pandemic could be a challenge in the care of diabetes. Our data, though limited, have shown that the answers to the questions above do have the potential to change

clinical practice during the ongoing pandemic period too.

Author Contributions

AVC: design, conducted data collection, analysis and manuscript writing. DP: design, manuscript writing. AD, SM and FS: data collection and analysis. IC, SB, and AB: revised the manuscript for critical content. All the authors approved the final version of the work to be published.

Novelty Statement

The novelty of the data presented lies in having explored not only the covid19 impact during the first wave pandemic, i.e., risk of infection, hospitalization and death, in a large population of people with diabetes living in a province of Central North Italy (the first European country where SARS-Cov 2 did spread) but also because we explored if there were different risks between type 1 and type 2 diabetes, and between the type of antidiabetic drugs. Furthermore, the data could impact current clinical practice to improve drug prescriptions for people with type 2 diabetes during the ongoing coronavirus pandemic

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