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RESEARCH ARTICLE

Association of anti-diabetic drugs and covid-19 outcomes in patients with diabetes mellitus type 2 and chronic kidney disease: Nationwide registry analysis

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Abstract

Introduction

Patients with diabetes mellitus type 2 and chronic kidney disease (T2DM-CKD) have a 5 times higher risk of developing severe SARS-CoV-2 infection than those without these 2 diseases. The goal of this study is to provide information on T2DM-CKD and COVID-19 outcomes, with an emphasis on the association with anti-diabetic medications.

Methodology

Study is designed as a retrospective cohort analysis covering the years 2020 and 2021. Data from the National Diabetes Registry (CroDiab) were linked to hospital data, primary healthcare data, Causes of Death Registry data, the SARS-CoV-2 vaccination database, and the SARS-CoV-2 test results database. Study outcomes were cumulative incidence of SARS-CoV-2 positivity, COVID-19 hospitalizations, and COVID-19 deaths. For outcome predictors, logistic regression models were developed.

Results

Of 231 796 patients with diabetes mellitus type 2 in the database, 7 539 were T2DM-CKD (3.25%). The 2-year cumulative incidences of all three studies' outcomes were higher in T2DM-CKD than in diabetes patients without CKD (positivity 18.1% vs. 14.4%; hospitalization 9.7% vs. 4.2%; death 3.3% vs. 1.1%, all p<0.001). For COVID-19 hospitalization, protective factors were SGLT-2 inhibitors use (OR 0.430; 95%CI 0.257–0.719) and metformin use (OR 0.769; 95% CI 0.643–0.920), risk factors were insulin use (1.411; 95%CI 1.167–1.706) and sulfonylureas use (OR 1.226; 95% CI 1.027–1.464). For SARS-CoV-2 positivity

protective factors were SGLT-2 inhibitors (0.607; 95% CI 0.448–0.823), repaglinide use (OR 0.765; 95% CI 0.593–0.986) and metformin use (OR 0.857; 95% CI 0.770–0.994). DPP-4 inhibitors showed a non-significant decrease in risk for COVID-19 death (OR 0.761; 95% CI 0.568–1.019).

Conclusion

T2DM-CKD are heavily burdened by COVID-19 disease. Our results suggest no association between antidiabetic drugs and COVID-19 death outcome while SGLT-2 and metformin show to be protective against COVID-19 hospitalization and infection, repaglinide against infection, and insulin and sulfonylureas show to be risk factors for COVID-19 hospitalization and infection. Further research in T2DM-CKD is needed.

Introduction

At the moment of this paper writing, COVID-19 is no longer defined as a Public Health Emergency of International Concern. However, it continues to take a significant toll on health globally due to the continued widespread circulation of the virus [1–3]. Also, it is estimated that at least 17 million people experienced Post COVID-19 Condition in the first 2 years of the pandemic and that number potentially doubled to over 34 million in 2022 [2].

Very early in the course of pandemics, it was clear that patients with comorbidities are in greater danger from developing more severe forms of COVID-19 disease than the otherwise healthy people [4–14]. This is especially true for patients with diabetes and patients with CKD [15, 16].

However, multimorbidity, the presence of two or more long-term health conditions, a major growing public-health challenge, makes the person even more prone to dying from COVID-19 [15, 17]. This is especially true for patients with diabetes mellitus type 2 and chronic kidney disease (T2DM-CKD) who have up to 7.22 times higher odds of severe infection in comparison to people without these 2 diseases [18].

Another topic that has been interesting to the scientific community and among clinicians is the effect of antidiabetic drugs on COVID-19 outcomes [19]. There were uncertainties if these drugs might lead to worse outcomes of COVID-19 in patients with diabetes [5, 19–28]. For the population of T2DM-CKD, antidiabetics with renoprotective effect and their association with COVID-19 outcomes might be of special interest—SGLT-2 inhibitors and GLP-1 analogues [15, 28].

Scientific activity analyzing associations of antidiabetics and COVID-19 outcomes in DM2 patients is live although no firm conclusions have been made yet. On the other hand, we found no studies conducted specifically on the heavily burdened T2DM-CKD population.

In our study, our goals were to:

1. Evaluate the prevalence of T2DM-CKD,
2. Evaluate the 2-year cumulative incidences (years 2020 and 2021) of SARS-CoV-2 infections, COVID-19 hospitalizations, and COVID-19 deaths among T2DM-CKD,
3. Analyze risk factors for SARS-CoV-2 infections, COVID-19 hospitalizations, and COVID-19 deaths in the observed population with a focus on anti-diabetic therapy.

Methodology

The study was a retrospective data analysis covering the period from, Jan 1st, 2020 to Dec 31st, 2021. Characteristics of the entire population of patients with diabetes mellitus type 2 in Croatia were analyzed, focusing on the sub-population of people with chronic kidney disease (T2DM-CKD).

Croatian National Diabetes Registry (CroDiab) was the source of data. CroDiab contains individual longitudinal data on patients with diabetes mellitus [29, 30]. Several sources are being used to feed CroDiab with data via the National Public Health Information System of Croatia and the Central Health Information System of the Republic of Croatia: clinical laboratories, primary health care providers, and hospitals [31, 32]. For our study, CroDiab was linked to a database containing SARS-CoV-2 test results, the National Vaccination Database (eVac), and the National Causes of Death Registry using a common personal identifier [33, 34]. The resulting data export was anonymized.

CroDiab Registry was accessed for research purposes on January 1st 2022. Authors PI and TB had access to personal patient identifiers during data collection. They anonymized the data and then sent it to JD for data analysis. All other authors had access to aggregated data only.

The outcome of SARS-CoV-2 infection was defined as the first or only positive test result (nasopharyngeal swab, Polymerase Chain Reaction (PCR)). According to hospital data, COVID-19 hospitalization outcome was defined as a hospitalization with COVID-19 being the primary or secondary diagnosis. COVID-19 death outcome was defined as death with COVID-19 listed as the primary source of death per the National Causes of Death Registry. The diagnosis of COVID-19 was determined per the World Health Organization International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), code U07. All COVID-19 diagnoses were laboratory-confirmed by PCR test.

Anti-diabetic drug intake was defined as a prescription that was prescribed at least two times in eight months before the SARS-CoV-2 or COVID-19 outcome. If the person experienced none of the outcomes, therapy was defined if a prescription was picked up at least once eight months before the patient visited her primary healthcare provider with a diagnosis of diabetes mellitus recorded in the system during that visit. Glycated hemoglobin (HbA1C) and body mass index (BMI) data were searched and retrieved six months before outcomes or primary health care visits.

A person is classified as a person with diabetes mellitus if at least one of the following conditions are met: (1) at least one hospital report with diabetes mellitus diagnosis was found in the system, (2) if the person visited their primary healthcare provider at least twice in period of study and ICD-10 diagnosis of E11 was recorded during the visits, (3) if the person was prescribed at least two prescriptions with diagnosis E11 or if the prescriptions had Anatomical Therapeutic Chemical Classification (ATC) codes A10 excluding code A10BA, (4) if person's primary healthcare provider reported the person as diabetes mellitus patient via the National Public Health Information System plus the person visited her primary healthcare provider at least once and ICD-10 diagnosis of E11 was recorded during the visit or the person was prescribed at least one prescription with diagnosis E11 or if the prescription had ATC codes A10 excluding code A10BA [35].

Chronic kidney disease was defined as ICD-10 diagnosis N18 (Chronic Kidney Disease) and/or E11.21 (Type 2 Diabetes Mellitus with Diabetic Nephropathy) recorded at least twice in the system from Jan 1st 2018 onwards.

Individual comorbidities were identified if their ICD-10 codes were recorded at least twice in the system from Jan 1st 2018 onwards. ICD-10 codes searched for were as follows: malignant neoplasms (C00-C97); hypertensive diseases (I10-I15); ischemic heart diseases (I20-I25);

cerebrovascular diseases (I60-I69); diseases of the circulatory system excluding hypertension (I00-I09 and I20-I99); chronic lower respiratory diseases (J40-J47); other chronic obstructive pulmonary disease (J44); cardiomyopathy (I48).

Inclusion criteria for data analysis were type 2 diabetes mellitus, defined as per CroDiab definition already described, and age of 18 years or above. The exclusion criteria were lack of reliable data on anti-diabetic drug use. The latter patients were omitted from the analysis.

Statistical analysis

Differences between groups of individual conditions were compared with the $\chi 2$ test. The level of significance was set at $\alpha = 0.05$.

Logistic regression analysis was used to determine the relative risks of developing outcomes. Initially, the model included all available variables. In the final model, selected variables were included. Variables were selected using the backward stepwise Likelihood Ratio (LR) method. In the multiple models, Odds ratios (OR) and 95% Confidence Intervals (CI) were determined.

In our initial statistical analysis plan, these covariates were systematically forced into the models: age, sex, BMI and HbA1c, type 2 diabetes mellitus duration, ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB) intake, SARS-CoV-2 vaccination data, comorbidities, and anti-diabetic drugs. However, models with BMI and HbA1b could not perform due to the deficient number of BMI and HbA1c data available, so these variables were not included in further models.

Analyses were performed with IBM SPSS Statistics software, version 29.0 (IBM, Armonk, NY, USA).

Ethics

The Croatian Institute of Public Health Ethical Committee (No. 381-15-21-3) and the University of Zagreb, School of Medicine Ethical Committee (No. 641-01/22-02/01) approved the study. The need for informed consent was waived by The Croatian Institute of Public Health Ethical Committee. The study has been performed in accordance with the Declaration of Helsinki.

Results

There were 310 749 patients with diabetes mellitus type 2 in the CroDiab database older than 18 years of age. After excluding patients without reliable anti-diabetic therapy data (N = 78 953), we were left with 231 796 patients. Out of these, 7 539 had chronic kidney disease (prevalence 3.25%). Table 1 shows the demography and characteristics of these patients.

T2DM-CKD were predominantly male, of old age, with a mean diabetes duration of almost 8 years. Almost all of them have hypertensive diseases and 3/4 have circulatory diseases, 1/3 have ischemic heart disease, 1/4 have cardiomyopathy and 1/4 have a chronic respiratory disease. Forty percent are taking metformin or/and sulfonylurea and 1/3 are taking a DPP-4 inhibitor. One-fourth is treated with insulin. Sixty six percent have received at least one dose of the SARS-CoV-2 vaccine while only about 30% have received a booster. The use of SGLT-2 inhibitors, GLP-1 analogues, pioglitazone, repaglinide and acarbose is below 10%. Two-year cumulative incidence of SARS-CoV-2 infections was 18.1%, COVID-19 hospitalizations 9.7%, and COVID-19 deaths 3.3%.

SARS-CoV-2 and COVID-19 epidemiology in T2DM-CKD is compared with the epidemiology of the diabetic patients without CKD in Table 2.

Table 1. Characteristics of patients with diabetes mellitus type 2 and chronic kidney disease (N = 7539).

Demography	Male sex, N (%)	4305 (57.1%)
	Age in years. mean ± SD	73.27±9.35
	Diabetes duration in years. mean ± SD	7.73±4.64
COVID-19 outcomes	SARS-Cov-2 positive, N (%)	1363 (18.1%)
	COVID-19 hospitalized, N (%)	731 (9.7%)
	COVID-19 deaths, N (%)	251 (3.3%)
ACEI	Yes, N (%)	3415 (45.3%)
ARB	Yes, N (%)	617 (8.2%)
SARS-CoV-2 vaccination	Dose 1, N (%)	5039 (66.8%)
	Dose 2, N (%)	4752 (63%)
	Booster, N (%)	2429 (32.2%)
Comorbidities other than chronic kidney disease	Hypertensive diseases, N (%)	7023 (93.2%)
	Diseases of the circulatory system excluding hypertension, N (%)	5741 (76.2%)
	Ischaemic heart diseases, N (%)	2740 (36.3%)
	Cardiomyopathy, N (%)	1742 (23.1%)
	Chronic lower respiratory diseases, N (%)	1477 (19.6%)
	Cerebrovascular diseases, N (%)	1356 (18%)
	Malignant neoplasms, N (%)	1287 (17.1%)
	Other chronic obstructive pulmonary disease, N (%)	1043 (13.8%)
Diabetes mellitus chronic treatment	Biguanides (metformin), N (%)	3016 (40%)
	Sulfonylureas, N (%)	2884 (38.3%)
	DPP-4 inhibitors, N (%)	2463 (32.7%)
	Insulin, N (%)	2004 (26.6%)
	GLP-1 analogues, N (%)	596 (7.9%)
	Meglitinides (repaglinide), N (%)	505 (6.7%)
	SGLT-2 inhibitors, N (%)	447 (5.9%)
	Thiazolidinediones (pioglitazone), N (%)	400 (5.3%)
	Alpha glucosidase inhibitors (acarbose), N (%)	52 (0.7%)

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blockers. DPP-4 = Dipeptidyl peptidase 4. SGLT-2 = Sodium-glucose co-transporter 2. GLP-1 = Glucagon-like peptide-1

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T2DM-CKD patients have a 20% higher risk of acquiring SARS-CoV-2 infection, more than double the risk of getting hospitalized due to COVID-19, and 3 times the risk of dying from COVID-19 in comparison to the diabetes mellitus type 2patients without CKD.

Table 3 shows outcomes in patient groups according to different antidiabetic drug use.

Table 2. SARS-CoV-2 and COVID-19 epidemiology in the studied cohort, comparison to diabetes mellitus type 2 patients without chronic kidney disease.

Outcome	T2DM-CKD (N = 7539)	T2DM no CKD (N = 224 257)	P
SARS-CoV-2 infections	1363 (18.1%)	32378 (14.4%)	<0.001
COVID-19 hospitalizations	731 (9.7%)	9460 (4.2%)	<0.001
COVID-19 deaths, N (%)	251 (3.3%)	2441 (1.1%)	<0.001

Years 2020 and 2021

P values calculated via hi square test

Abbreviations: T2DM-CKD = Patients with diabetes mellitus type 2 and chronic kidney disease; T2DM no CKD = Diabetes mellitus type 2 patients without chronic kidney disease

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Table 3. SARS-CoV-2/COVID-19 outcomes in patients with diabetes mellitus type 2 and chronic kidney disease depending on antidiabetic therapy.

Antidiabetic medication		COVID-19 outcomes		
		positivity	hospitalization	death
SGLT-2 inhibitor	Yes (N = 414)	**53 (11.9%)**	**16 (3.6%)**	**5 (1.1%)**
	No (N = 6904)	**1310 (18.5%)**	**715 (10.1%)**	**246 (3.5%)**
	p	**<0.001**	**<0.001**	**0.007**
metformin	Yes (N = 2843)	**496 (16.4%)**	**221 (7.3%)**	**83 (2.8%)**
	No (N = 4475)	**867 (19.2%)**	**510 (11.3%)**	**168 (3.7%)**
	p	**0.003**	**<0.001**	**0.022**
sulfonylureas	Yes (N = 2824)	543 (18.8%)	**310 (10.7%)**	100 (3.5%)
	No (N = 4494)	820 (17.6%)	**421 (9%)**	151 (3.2%)
	p	0.184	**0.015**	0.599
DPP-4 inhibitors	Yes (N = 2403)	426 (17.3%)	223 (9.1%)	**68 (2.8%)**
	No (N = 4915)	937 (18.5%)	508 (10%)	**183 (3.6%)**
	p	0.218	0.189	**0.055**
GLP-1 analogues	Yes (N = 565)	105 (17.6%)	**42 (7%)**	14 (2.3%)
	No (N = 6753)	1258 (18.1%)	**689 (9.9%)**	237 (3.4%)
	p	0.76	**0.023**	0.164
acarbose	Yes (N = 48)	9 (17.3%)	5 (9.6%)	3 (5.8%)
	No (N = 7270)	1354 (18.1%)	726 (9.7%)	248 (3.3%)
	p	0.885	0.984	0.325
pioglitazone	Yes (N = 388)	69 (17.3%)	36 (9%)	14 (3.5%)
	No (N = 6930)	1294 (18.1%)	695 (9.7%)	237 (3.3%)
	p	0.658	0.629	0.845
repaglinide	Yes (N = 495)	79 (15.6%)	48 (9.5%)	13 (2.6%)
	No (N = 6823)	1284 (18.3%)	683 (9.7%)	238 (3.4%)
	p	0.141	0.88	0.327
insulin	Yes (N = 1954)	**400 (20%)**	**239 (11.9%)**	**89 (4.4%)**
	No (N = 5364)	**963 (17.4%)**	**492 (8.9%)**	**162 (2.9%)**
	p	**0.011**	**<0.001**	**0.001**

P calculated via hi square test

statistically significant p values are bolded

Patient characteristics for each group are presented in S1 Table

Abbreviations: SGLT-2 = Sodium-glucose Cotransporter-2, DPP-4 = Dipeptidyl Peptidase 4, GLP-1 = Glucagon-like peptide 1

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T2DM-CKD taking SGLT-2 inhibitors or metformin had lower incidences of all 3 study outcomes in comparison to patients not taking these drugs. Patients treated with insulin got infected, hospitalized, and died more often than patients not treated with insulin. The sulfonylurea-group had a higher incidence of hospitalizations, while the GLP-1-analogues-group had a lower incidence of hospitalizations. Patients in DPP-4 inhibitors group died less often than patients not taking DPP-4 inhibitors, however P value is of borderline significance (0.055). Patient differences regarding demography, comorbidities, ACEI or ARBs intake, and SARS-CoV-2 vaccination status are presented in S1 Table.

Results of logistic regression models

SARS-CoV-2 positivity. The results of a multivariate regression model for the outcome of positivity are shown in Table 4.

Table 4. Multivariate regression model for SARS-CoV-2 positivity, patients with diabetes mellitus type 2 and chronic kidney disease (N = 7539).

Variable	p	Odds Ratio	95% Confidence Interval
Age in years	**0.004**	**0.990**	**0.984–0.997**
Female sex	**0.001**	**0.814**	**0.719–0.923**
Diabetes duration in years	**<0.001**	**1.024**	**1.011–1.037**
SGLT-2 inhibitors	**0.001**	**0.607**	**0.448–0.823**
metformin	**0.040**	**0.875**	**0.770–0.994**
repaglinide	**0.039**	**0.765**	**0.593–0.986**
SARS-cov-2 vaccination dose 1	**0.004**	**1.476**	**1.136–1.919**
SARS-cov-2 vaccination dose 2	**0.004**	**0.677**	**0.521–0.88**
SARS-cov-2 vaccination booster	**<0.001**	**0.276**	**0.231–0.330**
Chronic lower respiratory diseases	**0.043**	**1.163**	**1.005–1.347**

Final model, backward stepwise Likelihood Ratio (LR) method; P of the final model <0.001

The bolded text in the table represents variables with statistically significant association with outcome

Abbreviations: SGLT-2 = Sodium-glucose co-transporter 2

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Initially, the model included all available variables (variables from Table 1). In the final model, selected variables were included, as presented in Table 4. Variables were selected using the backward stepwise Likelihood Ratio (LR) method.

For SARS-CoV-2 infections, protective factors were older age, female sex, SGLT-2 inhibitors use, metformin use, repaglinide use, and 2nd and 3rd vaccine doses. Duration of diabetes was a risk factor as well as first dose of vaccine and presence of chronic lower respiratory disease.

COVID-19 hospitalization. The results of a multivariate regression model for the outcome of hospitalization are shown in Table 5.

Initially, the model included all available variables (variables from Table 1). In the final model, selected variables were included, as presented in Table 5. Variables were selected using the backward stepwise Likelihood Ratio (LR) method.

For COVID-19 hospitalizations, female sex, SGLT-2 use, metformin use, and 2nd and 3rd vaccine doses were protective factors. Insulin use, sulfonylurea and presence of diseases of the circulatory system excluding hypertension were risk factors.

Table 5. Multivariate regression model for COVID-19 hospitalizations, patients with diabetes mellitus type 2 and chronic kidney disease (N = 7539).

Variable	P	Odds Ratio	95% Confidence Interval
Female sex	**<0.001**	**0.71**	**0.604–0.833**
Insulin	**<0.001**	**1.411**	**1.167–1.706**
SGLT-2 inhibitors	**0.001**	**0.43**	**0.257–0.719**
Sulfonylureas	**0.024**	**1.226**	**1.027–1.464**
Metformin	**0.004**	**0.769**	**0.643–0.92**
SARS-cov-2 vaccination dose 2	**<0.001**	**0.554**	**0.465–0.66**
SARS-cov-2 vaccination booster	**<0.001**	**0.275**	**0.209–0.364**
Diseases of the circulatory system excluding hypertension	**0.023**	**1.264**	**1.033–1.546**

Final model, backward stepwise Likelihood Ratio (LR) method, P of the final model <0.001

The bolded text in the table represents variables with statistically significant association with outcome

Abbreviations: SGLT-2 = Sodium-glucose co-transporter 2

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Table 6. Multivariate regression model for COVID-19 death, patients with diabetes mellitus type 2 and chronic kidney disease (N = 7539).

Variable	P	Odds Ratio	95% Confidence Interval
Age in years	**0.002**	**1.024**	**1.009–1.040**
Female sex	**<0.001**	**0.548**	**0.417–0.721**
Diabetes duration in years	**<0.001**	**1.049**	**1.020–1.080**
Insulin	0.071	1.314	0.977–1.767
DPP-4 inhibitors	0.067	0.761	0.568–1.019
Repaglinide	0.094	0.610	0.342–1.088
SARS-cov-2 vaccination dose 2	**<0.001**	**0.188**	**0.131–0.271**
SARS-cov-2 vaccination booster	**<0.001**	**0.073**	**0.022–0.237**

Final model, backward stepwise Likelihood Ratio (LR) method, P of the final model <0.001

The bolded text in the table represents variables with statistically significant association with outcome

Abbreviations: DPP-4 = Dipeptidyl peptidase 4, SGLT-2 = Sodium-glucose co-transporter 2

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COVID-19 deaths. The results of a multivariate regression model for the outcome of death are shown in Table 6.

Initially, the model included all available variables (variables from Table 1). In the final model, selected variables were included, as presented in Table 6. Variables were selected using backward stepwise Likelihood Ratio (LR) method.

For the outcome of COVID-19 death, our models showed protective factors are female sex, and 2nd and 3rd vaccine doses. Risk factors are older age and diabetes duration.

Discussion

To the best of our knowledge, this is the first paper describing the association of antidiabetic drugs and SARS-CoV-2 and COVID-19 outcomes in T2DM-CKD. This is an important topic because population with both T2DM and CKD is heavily burdened by COVID-19 and because role of antidiabetic drugs in COVID-19 outcomes has been a matter of debate since the beginning of the pandemic with fear they might lead to worse outcomes [5, 18–28].

Our key findings regarding the association between antidiabetic drugs and COVID-19 outcomes in population suffering T2DM and CKD are optimistic for most antidiabetic drugs. No association between antidiabetic drugs and COVID-19 death outcome was found. SGLT-2 inhibitors and metformin were shown to be protective against COVID-19 hospitalization and SARS-CoV-2 infections. Repaglinide also showed protection against the infection. Our study did find insulin and sulfonylurea to be risk factors for COVID-19 hospitalization, though. Nevertheless, all this is far from fears present at the beginning of COVID-19 pandemic.

We identified 7539 T2DM-CKD in our database which makes a prevalence of 3.25% in the population of patients with diabetes mellitus type 2. The prevalence of CKD in the general adult population is 10–15% which means our prevalence estimate is too low [8]. This is probably because diagnosis of CKD is often not recorded in medical records which consequently leads to low numbers of ICD codes N18 (Chronic Kidney Disease) and E11.21 (Type 2 Diabetes Mellitus with Diabetic Nephropathy) in public health databases [8, 36].

When it comes to the use of antidiabetic medications in our T2DM-CKDs, 40% of patients are taking metformin, 38.3% sulfonylureas, 32.7% DPP-4 inhibitors, 26.6% insulin 7.9% GLP-1 analogues, 6.7% repaglinide, 5.9% SGLT-2 inhibitors, 5.3% pioglitazone, 0.7% acarbose. These numbers are lower than Columbian data which describe 17% of T2DM-CKDs taking SGLT-2 inhibitors, 67.3% metformin, and 52.2% DPP-4 inhibitors [37]. GLP-1 analogues use

is a bit lower in Columbian study, 5.2% [37]. Our numbers, however, are much higher than the US data—they report initiation rates of 2.5% for SGLT-2 inhibitors, 3.7% for DPP-4 inhibitors, 2.31% for GLP-1 receptor analogues, 4% for insulin, and 5.5% for sulfonylureas in T2DM-CKD [38]. Another study focusing on SGLT-2 inhibitors and GLP-1 analogues prescription in T2DM-CKD noted that 12% and 10% of these patients are taking SGLT-2 inhibitors and GLP-1 analogues, respectively [39].

Novel antidiabetics have renoprotective effects—SGLT-2 and GLP-1 analogues [15, 28]. Therefore, one would expect somewhat higher rates of prescribing these drugs to T2DM-CKD. However, this is not the case, not just in Croatia but also worldwide. Scherntha-ner et al warned about the "*worldwide inertia to the use of cardiorenal protective glucose-lowering drugs (SGLT2i and GLP-1 RA) in high-risk patients with type 2 diabetes*" [40].

It should be noted that our data refer to years 2018–2021 and the US data years 2007–2019 [38]. This is all prior to SGLT-2 inhibitors gaining regulatory approvals for use in CKD (2021 dapagliflozin, 2023 empagliflozin) [41, 42].

When it comes to renoprotective drugs other than antidiabetics, 45% of our patients are taking an ACEI and 8.3% an ARB, total of 53.3%. In Columbian data, 67.2% of T2DM-CKD are taking ARB and 15.8% ACEI, total of 83% [37]. In the US on the other hand, 17.8% and 56%of T2DM-CKD are initiating ACEI and ARBs, total of 73.8% [38].

We can conclude that the use of renoprotective novel antidiabetics in our cohort is as low as in the rest of the world while our use of ACEI/ARBs is lower than the worldwide trends.

Our data showed T2DM-CKD experienced more SARS-CoV-2 infections, more COVID-19 hospitalizations, and more COVID-19 deaths in the years 2020 and 2021 in comparison to the diabetes mellitus type 2 patients without CKD. This is in line with what we expected [18].

When it comes to the association of antidiabetic drugs and COVID-19, we found no published studies on this patient population with which we could compare our data. We can only comment on the associations of antidiabetic drugs with the general DM2 population.

Our study identified SGLT-2 inhibitors as protective from COVID-19 hospitalization (OR 0.430; 95% CI 0.257–0.719), and SARS-CoV-2 infection (OR 0.607; 95% CI 0.448–0.823). In years 2021 and 2023 SGLT-2 inhibitors dapagliflozin and empagliflozin, respectively, have received EU and the US regulatory approvals for use in CKD since they improve kidney outcomes regardless of their effect on HbA1c levels [41, 42]. The 2022 update of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for diabetes management in chronic kidney disease recommends the initiation of treatment with an SGLT-2-inhibitor in people with DM type 2 and CKD. By this, SGLT-2-inhibition has been established as a first-line treatment in individuals with DM type 2 and renal disease [43]. This could explain the potential protective effect shown in our cohort.

A meta-analysis and meta-regression conducted specifically to assess SGLT-2 inhibitors in diabetes patients with COVID-19 of a total of 17 studies showed that preadmission use of SGLT-2 inhibitors was associated with reduced mortality and severity of COVID-19. This benefit of SGLT-2 inhibitors on COVID-19 mortality was not significantly affected by patient factors such as age, sex, hypertension, heart failure, HbA1c levels, metformin use, duration of diabetes, and BMI. The paper's authors suggested SGLT-2 inhibitors could be considered an anti-diabetic drug of choice, especially during the pandemic [44]. Another, Bayesian meta-analysis of 35 studies on several anti-diabetic agents found that SGLT-2 inhibitors could reduce COVID-19 mortality risk in individuals with diabetes [45].

We would like to stress our focus is the use of SGLT-2 inhibitors prior to acquiring COVID-19 infection (pre-admission use) and not use during acute COVID-19 infection since it is known SGLT-2 inhibitors use during acute infection could be related to ketoacidosis [28].

Our study identified repaglinide as potentially protective against SARS-CoV-2 infections (OR0.756; 95% CI 0.593–0.986). We found a non-clinical study that identified repaglinide as one of the potential candidates for the treatment of COVID-19 [46].

Metformin use was identified in our study as protective from COVID-19 hospitalization (OR 0.769; 95% CI 0.643–0.920) and SARS-CoV-2 infection (OR 0.875; 95% CI 0.770–0.994). We found several large meta-analyses regarding metformin's protective association against COVID-19 death and hospitalization risk [47–49].

Our study did not identify GLP-1 analogues to have any kind of role in COVID-19 outcomes. This comes as a bit of a surprise since GLP-1 analogues have cardiovascular and somewhat renoprotective effects [15]. Some studies have shown protection from COVID-19 mortality in patients with T2DM2 [50]. Recently their use has shown promising effects in reducing excessive inflammation-induced acute lung injury and improving COVID-19 outcomes [51]. In addition to stimulating postprandial insulin secretion, GLP-1 receptor analogues also seem to have beneficial properties such as anti-inflammatory, anti-obesogenic, pulmonary protective effects, and gut microbiome modulating effects [52].

Our study did not identify any association between pioglitazone and acarbose and COVID-19 outcomes. In a meta-analysis, a thiazolidinedione and an alpha-glucosidase inhibitor were also found to be mortality-neutral in patients with diabetes mellitus type 2 and COVID-19 [53].

Our multivariate regression models showed DPP-4 inhibitors were associated with statistically non-significant decrease in odds for COVID-19 death (OR 0.761; 95% CI 0.568–1.019). Some studies have shown DPP-4 inhibitors mortality benefits in diabetic patients with COVID-19 [54]. DPP-4 inhibitors might inhibit entry of the virus, inhibit inflammation and fibrosis [54]. However, several studies have shown negative associations in terms of increased mortality risk and intensive care unit (ICU) admission risk for people who use them [27, 55].

Our data showed use of insulin (OR 1.411; 95% CI 1.167–1.706) and sulfonylurea (OR 1.226; 95% CI 1.027–1.464) could be related to higher odds of COVID-19 hospitalizations. This is in line with the DM2 population data [23, 45, 47]. When it comes to insulin, it should be noted that in all cited meta-analyses insulin was shown to be independent predictor of COVID-19 mortality or hospitalization regardless of the age, sex, diabetes duration and gylcemic status [23, 45, 47]. The underlying mechanism for insulin's association with COVID-19 hospitalization and death outcomes is unclear [47].

Study limitations

Our study has several strengths and several limitations. We described the entire population of T2DM-CKD of the Republic of Croatia and not just a sample. Also, we provided information regarding other comorbidities that could affect COVID-19 outcomes, such as chronic obstructive pulmonary disease which is often not the case in before mentioned studies published in DM2 population.

The limitations of the study are retrospective and observational design. Further on, part of the population was excluded from the analysis due to no medication data. Also, HbA1c, and BMI data, could not be included in logistic regression models due to insufficient data, as well as CKD stage data we currently do not have access to. Also, we currently do not have access to albuminuria or glomerular filtration (GF) data and therefore we have missed to identify the patients who have kidney damage that does not qualify as ICD diagnosis N18 or E11.21. Not having access to patients' medical records and missing clinical data such as BMI, HbA1c, albuminuria, GF is a known drawback of working with public health databases [56].

Low availability of HbA1c and BMI data can to a certain extent be explained by the COVID-19 pandemic which has had a negative effect on the utilization of healthcare by

diabetes patients with decreased numbers of diabetes panels (one of the sources of HbA1c and BMI data) and decreased numbers of visits to primary healthcare providers for diabetes-related problems and diabetes patients who visited their primary healthcare provider [57].

The accuracy of the coding of ICD diagnoses is another issue inherent to working with public health databases. Since we do not have access to medical records, checking the coding manually would be out of the scope of this study.

Additionally, analyzed data were collected during 2020 and 2021, when the original SARS-CoV-2 was still dominant. Therefore our analysis results may not be applied to other SARS-CoV-2 variants.

Conclusion

In conclusion, the relationship between the use of antidiabetic drugs and COVID-19 outcomes is important in clinical practice and to policymakers because of the growing prevalence of both diabetes mellitus and CKD, the increasing use of glucose-lowering drugs with renoprotective effect, the higher COVID-19 mortality observed in patients with T2DM-CKD and the unpredictable waves of COVID-19 despite vaccines [15, 26]. Drugs such as SGLT-2 inhibitors, metformin, and repaglinide seem not only to be safe in the age of COVID-19 but also beneficial.

Further research in this patient population is needed. It would be beneficial to asses association between antidiabetic drugs combinations and COVID-19 outcomes as well as between combinations of antidiabetic medications with ACEIs/ARBs and statins and COVID-19 outcomes. Further on, constant improvements in the field of data availability in public health databases are necessary.

Supporting information

S1 Table. SARS-CoV-2 and COVID-19 outcomes and patient characteristics in groups depending on antidiabetic therapy.
(XLSX)

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