










COVID-19 and Diabetes Mellitus: Are there any Differences in Outcomes with Anti-Diabetic Drugs?

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ABSTRACT

Aim: This study aims to analyze the effect of diabetes and diabetes drugs on the outcome of COVID-19 patients.

Material and Methods: All the patients with diabetes hospitalized for COVID-19 between March 15, 2020 and June 15, 2020 at İstanbul University Faculty of Medicine were screened. Outcomes of the patients were compared with patients without diabetes.

Results: Among six hundred fourteen patients (59.8% male, n=367) there were 151 patients with diabetes (24.5%). Patients with diabetes were hospitalized longer than patients without (12.1±10.3 vs. 10.2±7.3, p=0.037 in days), had higher intensive care unit (ICU) hospitalization rate (20.5% (n=31) vs. 12.0% (n=56), p=0.016, OR:1.8 (1.1-2.9)) and mortality rate (15.8% (n=24) vs. 7.7% (n=36, p=0.007), OR:2.1(1.2-3.8)).

There was no difference in admission to ICU between patients who use metformin, basal insulin or bolus insulin regarding admission to ICU compared to patients who don't (p= 0.32, p=0.22 and p=0.64, respectively). No patient on sodium-glucose co-transporter-2 treatment was treated in ICU. Death rate didn't differ between patients regarding their treatment modalities.

Conclusion: Patients with diabetes had worse outcomes than non-diabetic patients, and according to our findings and no anti-diabetic drug has a beneficial or harmful effect.

Keywords: COVID-19, Diabetes medication, Sodium-glucose co-transporter-2, Metformin

Covid-19 ve Diyabet: Antidiyabetik İlaçlar ile Sonlanımlarda Fark Var mı?

ÖZ

Amaç: Bu çalışma, diyabet ve diyabet ilaçlarının COVID-19 hastalarının sonuçları üzerindeki etkisini analiz etmeyi amaçlamaktadır.

Gereç ve Yöntemler: 15 Mart 2020-15 Haziran 2020 tarihleri arasında İstanbul Üniversitesi İstanbul Tıp Fakültesi'nde COVID-19 nedeniyle hastaneye yatırılan tüm diyabet hastaları tarandı. Hastaların sonuçları diyabeti olmayan hastalarla karşılaştırıldı.

Bulgular: Altı yüz ondört hastanın (%59,8 erkek, n=367) 151 tanesi diyabet hastası (%24,5) idi. Diyabetli hastalar diyabeti olmayan hastalardan daha uzun süre hastanede yattı (12,1±10,3'e karşı 10,2±7,3 /gün p=0,037), diyabetlilerin yoğun bakım ünitesinde (YBÜ) yatış oranı (20,5% (n=31) ve 12,0% (n) =56), p=0,016, OR:1,8 (1,1-2,9)) ve ölüm oranları (%15,8 (n=24) ve %7,7 (n=36, p=0,007), OR:2,1(1,2-3,8)) daha yüksekti.

Metformin, bazal insülin veya bolus insülin kullanan hastaların YBÜ'e yatışı açısından kullanılmayanlara göre fark yoktu (sırasıyla p=0,32, p=0,22 ve p=0,64). Sodyum-glukoz kotransporter-2 tedavisi alan hiçbir hasta YBÜ'de tedavi edilmedi. Diyabet hastalarının ölüm oranı, aldıkları tedavi yöntemlerine göre hastalar arasında farklılık göstermedi.

Sonuç: Diyabetli hastalar diyabetik olmayan hastalara göre daha kötü sonuçlara sahipti ve bizim bulgularımıza göre hiçbir antidiyabetik ilacın yararlı veya zararlı etkisi yoktu.

Anahtar Sözcükler: COVID-19, Diyabet tedavisi, Sodyum glukoz kotransporter-2, Metformin

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INTRODUCTION

Novel coronavirus disease 2019 (COVID-19) has caused a global pandemic and affected millions of people worldwide (1). Patients with advanced age, co-morbidities and immunosuppression are reported to be at greater risk of morbidity and mortality (2,3). Whether diabetes poses a higher risk for disease progression, hospitalization and death is still at question.

Various reports have shown an increased risk of death from diabetes for COVID-19 patients. Guan et al. reported that there were more patients with diabetes in their cohorts who experienced serious illness than the normal population (4). Guo et al. has shown increased inflammatory response in patients with COVID-19 and diabetes compared to patients without (5). Guo et al. has reported increased mortality among patients with diabetes compared to patients with other co-morbidities (6).

As the first line pharmacologic treatment of diabetes, metformin is under investigation for its effects on COVID-19 patients (7,8). Insulin and other drug classes are tested for their impact on the outcome of COVID-19 patients. This study aims to analyze the effect of diabetes and diabetes drugs on outcome of COVID-19 patients.

MATERIALS and METHODS

Ethics

Approval for the study was obtained from both Turkish Ministry of Health (2020-05-14T12_59_48) and *-blinded for peer review* Faculty of Medicine Ethics Committee (rule number: 08/06/2020-91658). Rules of Helsinki Declaration were followed through the study.

Subjects

All the patients hospitalized for COVID-19 between March 15, 2020 and June 15, 2020 at *-blinded for peer review* Faculty of Medicine were screened. Patients demographic characteristics were recorded from their medical records and patient history in their files. Patients were excluded if they were younger than 18 years.

Patient files were screened for (1) diabetes drugs patients used until the hospitalization (drug changes necessary during the hospitalization were not included to the analysis), (2) hospitalization outcomes (discharge, intensive care unit (ICU), death etc.). Outcomes were compared with patients without diabetes (control group). Patients' admission laboratory data were compared regarding their diabetes status.

Statistical Analysis

Statistical analysis was performed using the SPSS software version 16. Normality of the variables were tested using visual (histogram) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test).. Kruskal-Wallis and Mann-Whitney U tests were conducted to compare parameters among groups. Pearson and Spearman correlation methods were used to test correlations. Chi square test was used to determine an association between two categorical values. And correlation of a nominal and a categorical data were analyzed with the Eta value. An overall 5% type-I error level was used to infer statistical significance.

RESULTS

Six hundred fourteen patients (59.8% male, n=367) were included. There were 151 patients with diabetes (24.5%). Patients with diabetes were significantly older than patients without (63.2 ± 12.5 vs. 55.4 ± 15.9 , $p < 0.001$ in years) (Table 1). At admission patients with diabetes had lower oxygen saturation level (93.0 ± 5.7 vs. 94.6 ± 4.2 , $p = 0.002$ in %), similar body temperature (37.1 ± 1.3 vs. 37.3 ± 0.9 , $p = 0.095$ in Celsius degree), higher systolic blood pressure (135 ± 20.0 vs. 129 ± 21.3 , $p = 0.003$ in mmHg) and higher respiratory rate (20.8 ± 5.1 vs. 19.5 ± 4.6 , $p = 0.008$ per minute) compared to controls (Table 1).

When patient outcomes were analyzed; patients with diabetes were hospitalized longer than patients without (12.1 ± 10.3 vs. 10.2 ± 7.3 , $p = 0.037$ in days), however there was no statistically significant difference between hospitalization days in ICU (26.5 ± 20.4 vs. 24.6 ± 19.0 , $p = 0.688$). No difference was observed between groups regarding days from hospitalization to ICU (1.5 ± 4.75 (IQR) vs. 2 ± 6 (IQR), $p = 0.159$). Patients with diabetes had higher ICU hospitalization rate (20.5 % (n=31) vs. 12.0% (n=56), $p = 0.016$, OR:1.8 (1.1-2.9)) and mortality rate (15.8% (n=24) vs. 7.7% (n=36, $p = 0.007$), OR:2.1 (1.2-3.8)).

Among patients with diabetes 103 patients (68%) had hypertension. Mean glucose level was 181.9 ± 73 mg/dL. Mean HbA1c percent was 7.2 ± 1.8 . Patients had a mean duration of diabetes as 8.9 ± 7.1 years. There were 29 patients (19%) with coronary heart disease and 21 patients (14%) with heart failure. ICU admission rate and death rate were 20.5 % (n=31) and 15.9% (n=24), respectively. A hundred and five patients (69.5 %) were on metformin treatment, 35 patients (23.1 %) on basal insulin and 21 (13.9%) patients on basal and bolus insulin treatment (Table 2). Only 8 patients were on pre-mixed insulin treatments. There were 37 patients (24.5%) on statin treatment. No difference was observed in terms of outcomes between statin users and non-users.

Table 1: Comparison of preadmission laboratory parameters of patients with and without diabetes.

Parameters	DM (n=151)	Non-DM (n=463)	P value
Age, years	63.2±12.5	55.4±15.9	<0.001
Duration of hospitalization, days	12.1±10.3	10.2±7.3	0.03
Duration of ICU, days	26.5±20.4	24.6±19.0	0.68
Height, cm	166.0±8.1	167.9±9.7	0.40
Body weight, kg	82.5±14.1	82.1±14.8	0.98
Body mass index, kg/m ²	30.5 ±5.8	28.8±4.4	<0.01
Body temperature, °C	37.1±1.3	37.3±0.9	0.60
SpO ₂ , %	93.00±5.7	94.64±4.2	<0.001
Systolic blood pressure, mmHg	135.20±20.1	129.20±21.3	<0.01
Diastolic blood pressure, mmHg	78.4±12.4	77.3±11.8	0.28
Pulse rate	95.20±16.9	95.18±13.4	0.05
Respiratory rate	20.8±5.1	19.5±4.6	0.03
pH	7.40±0.08	7.40±0.07	0.35
pO ₂ , mmHg	66.78±16.1	62.71±15.3	0.38
pCO ₂ , mmHg	38.67±8.7	40.61±8.6	0.81
HCO ₃ , mEq/L	23.11±3.7	24.19±3.2	0.14
Lactate, mEq/L	2.22±2.2	1.77±1.1	<0.001
Hemoglobin, gr/L	12.24±2.1	12.94±2.0	0.89
Platelet, 10 ⁶ /L	240942±102395	227813±93060	0.07
Leukocyte, 10 ⁶ /L	8535±9587	7108±3480	<0.001
Creatinine, mg/dL	1.02±0.4	1.11±1.2	0.09
Sodium, mEq/L	136.74±4.3	137.93±4.9	0.67
Potassium, mEq/L	4.39±0.5	4.50±5.0	0.57
Fasting plasma glucose, mg/dL	172.9±72.8	118.7±42.8	<0.001
Aspartate aminotransferase, IU/L	34.49±34.2	36.22±32.1	0.92
Alanine aminotransferase, IU/L	30.64±46.1	33.10±46.5	0.70
Lactate dehydrogenase, U/L	281.42±111.9	279.84±135.2	0.60
Albumin, g/dL	3.83±0.5	3.92±0.5	0.37
Triglyceride, mg/dL	123.71±72.8	121.42±71.2	0.63
Procalcitonin, ng/mL	0.46±1.5	0.62±3.9	0.31
Ferritin, mg/L	475.49±654.4	805.20±4016.8	0.22
D-dimer, ng/mL	1715±2694	1492±2289	0.42
Troponin, ng/mL	41.85±125.2	33.75±185.9	0.67
CRP, mg/L	74.31±66.9	70.83±78.5	0.44

CRP: C-reactive protein, DM: Diabetes mellitus.

There was no difference in admission to ICU between patients who use metformin and patients who don't (p=0.32), (Table 3). No difference was observed between patients who use basal insulin or bolus insulin regarding admission to ICU compared to patients who don't use these agents (p=0.22 and p=0.64, respectively). No patient on

SGLT-2 inhibitor treatment (12 patients were on SGLT-2 inhibitor treatment) was treated in ICU. Death rate didn't differ between patients who use metformin, basal insulin, bolus insulin, pioglitazone, sulfonylureas, DPP-4 inhibitors and SGLT-2 inhibitors (Table 3).

DISCUSSION

This study reports that death and ICU admission rate of patients with diabetes were significantly higher than patients without diabetes in a university hospital.

Outcomes of COVID-19 patients with diabetes differ significantly according to region, country, ethnicity and available treatments. A cohort from a New York Hospital reports (9) death rate as 10.2%, whereas another report from USA with a cohort from different states (10) has higher death rate as 28%. In a report from Italy this rate is as high as 48% (11). Their cohort was relatively older than our patients. Our death rate is 15,8% among patients with diabetes and it's almost twice the rate of patients without diabetes. A meta-analysis with 83 studies has revealed two-fold increase in severe/clinical illness (12) compatible with our results and our OR.

Also, because our cohort is from a tertiary university hospital where our control patients (patients without diabetes) had other morbid disorders such malignancies,

chronic kidney disease etc., these results can be interpreted as an understatement of the real risk. Holman et al. showed increased mortality rate with HbA1c levels > 7.6% compared to levels lesser(13). In our study mean HbA1c was 7,2%. This could have also affected our results.

Patients on metformin did not have different mortality or morbidity rate compared to patients without this treatment. Role of metformin on COVID-19 related morbidities is not clear yet. There are reports of improved outcomes with metformin as well as without significant difference (14). SGLT-2 inhibitors are also among drugs which are under attention. Dalan et al. reported lower risk of mechanical ventilation with SGLT-2 inhibitors (15). Whether this beneficial effect is the result of cardiovascular protection obtained with these agents or an unknown pleiotropic effect, is the question of a larger randomized trial. There is an ongoing clinical trial to investigate the effects of dapagliflozin in COVID-19 which can hopefully address these inquiries and calculate euglycemic ketoacidosis risk with these agents can bring to COVID-19 infection. In our study patients on SGLT-inhibitors had relatively lower rate of ICU admission and mortality, however this difference didn't reach statistical significance due to small sample size.

In our cohort insulin use was not associated with better or worse outcomes. Yu et al. has reported that insulin use was associated with enhanced inflammation (16). Riahi et al. has reported that insulin therapy increased mortality risk in both inpatients and outpatients (17). These findings are not unexpected due to the conditions in which insulin is used. Patients on insulin are often patients with poor glycemic control and/or patients with advanced age and diabetes duration in need for insulin therapy.

DPP-4 inhibitors had no effect on mortality or ICU admission. Our cohort had relatively small number of

Table 2: Frequency of anti-diabetic drug classes.

Anti-Diabetic Drugs	Case proportions (Total n=151)	
	n	%
Metformin	105	69.5
Basal insulin	35	23.1
Bolus insulin	21	13.9
Pre-mixed insulin	8	5.0
Pioglitazone	10	6.6
DPP-4 inhibitors	29	19.2
Sulfonylureas	32	21.1
SGLT-2 inhibitors	12	7.9

DPP-4: Dipeptidyl peptidase-4, SGLT-2: Sodium Glucose Co-transporter.

Table 3: Outcomes with different anti-diabetic drug classes.

Outcomes	ICU Admission Rate					Mortality Rate				
	Treated with		Treated without		P	Treated with		Treated without		P
	n	%	n	%		n	%	n	%	
Metformin	18	62	11	38	0.321	15	62.5	9	37.5	0.414
Basal insulin	4	13.7	25	86.3	0.183	4	16.6	20	83.4	0.410
Bolus insulin	4	13.7	25	86.3	0.984	4	16.6	20	83.4	0.670
Pioglitazone	3	10.3	26	89.7	0.595	4	16.6	20	83.4	0.085
DPP-4 inhibitors	6	20.6	23	79.4	0.72	3	12.5	21	87.5	0.176
Sulfonylurea	2	6.9	27	93.1	0.12	4	16.6	20	83.4	0.823
SGLT-2 inhibitors	0	0	29	100	0.11	2	8.3	22	91.7	0.98

ICU: Intensive care unit, DPP-4: Dipeptidyl peptidase-4, SGLT-2: Sodium glucose co-transporter.

patients on DPP-4 inhibitors (n=29, 19%) which may have lowered its impact on analysis. Solerte et al. has suggested that gliptins may reduce virus entry and replication in a molecular level (18). From real life data, Strollo et al. has reported no difference with DPP-4 inhibitors in prevention or progression of COVID-19 (19).

Limitations of our trial include observational nature of the study. Also, our results are from a tertiary unit, therefore our results may not be reflecting general population. Our analysis includes drugs used in preadmission, thus any changes of diabetes drugs during COVID-19 therapy is not reflected in our report.

As a result, diabetic patients had worse outcomes than non-diabetic patients, and according to our findings and no anti-diabetic drug has a beneficial or harmful effect.

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Author Contributions

Concept: **Ramazan Çakmak**, Design: **Ramazan Çakmak**, Data Collection or Processing: **Vefa Seferova Nasifova**, **Alpay Medetalibeyoğlu**, **Yunus Çatma**, **Naci Şenkal**, **Murat Köse**, Analysis or Interpretation: **Özge Telci Çaklılı**, **Ramazan Çakmak**, Literature Search: **Ümmü Mutlu**, **Ayşe Merve Ok**, **Gökтуğ Sarıbeyliler**, Writing: **Ramazan Çakmak**, **Özge Telci Çaklılı**.

Conflict of Interest

The authors declare that they have no competing interest.

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Ethical Approve

The Ministry of Health approval for the study was received on 19.05.2020 with the approval number 2020-05-14T12_59_48. Approval was obtained from the Ethics Committee of Istanbul Faculty of Medicine on 21.05.2020.

Peer-Review Process

Extremely peer-reviewed and accepted.

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