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Analysis of the Effect of Hypoglycemic Therapy Preceding COVID-19 on Its Course and Outcomes

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Abstract **Aim:** to study the effect of glucose lowering therapy received by patients with diabetes on the course and outcome of COVID-19. **Materials and methods.** We analyzed a cohort of patients with type 1 diabetes (213 patients) and type 2 diabetes (763 patients) who had COVID-19 in 2020. Of these, 234 patients (120 men (51.28%) and 114 women (48.72%)) were selected, in whom hypoglycemic therapy did not change for at least 6 months preceding the coronavirus infection. **Results.** In our study, correlation analysis did not show significant links between the hypoglycemic drugs taken and the course of coronavirus infection. Patients with type 2 diabetes treated with insulin had a high risk of pneumonia (9,656, 95% CI 1,260-73,979). Patients with type 2 diabetes who received insulin or SU were more likely to need hospitalization. The risk of death, the severity of COVID-19 and the need for dexamethasone administration did not depend on the type of hypoglycemic therapy received. **Conclusion:** treatment of patients with diabetes should be based on the current recommendations, and no matter, what glucose lowering drug is used, achieving glycemic control is key factor to prevent complications.

Keywords Diabetes, COVID-19, Glucose-lowering therapy

1. Introduction

Despite the abundance of scientific papers devoted to the peculiarities of the course of coronavirus infection in patients with diabetes mellitus, despite the end of the COVID-19 pandemic, there is still no consensus and uniform standards for hypoglycemic therapy of patients with diabetes in the acute period of coronavirus infection. The majority of recommendations include suspense of any non-insulin drugs in patients with severe infection. While how safe is to prescribe non-insulin glucose lowering agents to patients with non-severe COVID-19 is still a matter of discussion.

Taking into account that at the beginning of the COVID-19 pandemic, all recommendations were based on the experience gained during the first pandemic caused by the MERS virus, a detailed analysis of hypoglycemic therapy and its effect on the course of coronavirus infection seems to us an urgent task. So, we aimed to study the effect of glucose lowering therapy received by patients with diabetes on the course and outcome of COVID-19.

2. Materials and Methods

We performed cross-sectional study, where we analyzed a cohort of patients with type 1 diabetes (213 patients) and type 2 diabetes (763 patients) who had COVID-19 in 2020 in Tashkent. Sampling was full based on the database of COVID-19 patients of Tashkent state Healthcare Department which included all patients who had confirmed COVID-19 since 2020. Of these, data of 234 patients (120 men (51.28%) and 114 women (48.72%)) were selected, in whom hypoglycemic therapy did not change for at least 6 months preceding the coronavirus infection. 22 patients were patients with type 1 diabetes, 181 were patients with type 2 diabetes. Inclusion criteria were: having type 1 or type 2 diabetes diagnosed before 2020, confirmed COVID-19 by rPCR and medical records. Exclusion criteria: changing in glucose-lowering therapy within the last 6 months before the study, pregnancy in 2020 or later.

Considering that all patients with type 1 diabetes received insulin, they were included in the subgroups of people who received human or analog insulins for analysis. The average age of patients was 56.89±13.50. The average duration of diabetes was 8.43±5.81 years. The average BMI was 31.64±6.27 kg/m^2, while normal BMI was in 8.62% of patients, overweight – 3 15.52%, obesity of the 1st degree – in 58.62%, obesity of the 2nd degree – in 12.07% and obesity of the 3rd degree – in 5.17% of patients.

The average blood pressure was 154.60±17.87 / 93.80±10.86 mm Hg. At the same time, 64.96% of patients had hypertension, and 60.68% had ischemic heart disease.

14.96% had a mild course of coronavirus infection,

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58.97% - moderate-severe, 26.07% - severe. 65.38% were hospitalized in the acute period of coronavirus infection. The average duration of hospitalization during the acute period of COVID-19 was 8.68±1.95 days. 73.93% had pneumonia, 65.81% of patients received dexamethasone. 5 (2.14%) patients died, average age was 58.8±8.93 years. Of the deceased patients, 4 were men, 1 with type 1 diabetes, all with grade 1 obesity, duration of diabetes from 1 to 10 years (average duration of diabetes 6.25 ± 3.30 years), two received metformin (1 – in combination with human insulins, 1 – in combination with analog insulins and iDPP-4), two – SU, one (patient with type 1 diabetes) – analog insulins. All the deceased had a severe course of coronavirus infection with bilateral pneumonia, while only three were hospitalized (the average length of hospital stay was 7.5± 3.32 days), two patients received dexametazone.

In total, patients received the following hypoglycemic drugs (as mono- and combination therapy): 44.9% of patients received metformin therapy, although in national standards for the treatment of type 2 diabetes, metformin is a first-line drug and remains as a component of multicomponent therapy throughout the patient's management until eGFR decreases to 30 ml/min/1,73m2 [2; pp.1-132; 22; C. 1-301]. 36.4% of patients received human insulins, 13.7% - analog insulins, 28.2% – sulfonylureas, 8.6% of patients received iDPP-4. Only 1 patient received iSGLT2, so this drug was not included in the subsequent analysis.

3. Results

According to the groups of hypoglycemic drugs, patients did not differ in age or gender, patients taking iDPP-4 were a group of patients with a shorter history of diabetes (compared with patients receiving human insulins), a higher BMI (compared with all other groups), hospitalized for a longer period (compared with patients receiving human insulin). who received SU and human insulins). Patients receiving metformin had a higher BMI (compared with patients receiving insulin) and shorter hospitalization periods in the acute period of coronavirus infection (compared with patients receiving analog insulin).

To analyze the effect of hypoglycemic therapy preceding the onset of coronavirus infection on its course and outcomes, we analyzed the frequency of clinical manifestations of COVID-19 depending on the group of hypoglycemic drugs (Table 1).

Patients receiving metformin and human insulins had more pronounced clinical symptoms of coronavirus infection. The most common symptoms were general weakness, headaches, cough, shortness of breath, fever, chest pain.

For a deeper statistical analysis, we calculated the correlation coefficient of the severity of coronavirus infection and its symptoms with the groups of hypoglycemic drugs received (Table 2).

Correlation analysis did not show significant links between the hypoglycemic drugs taken and the course of coronavirus infection.

Therefore, further to study the possible effect of hypoglycemic therapy on the course and outcome of COVID-19, we conducted a logistic regression analysis.

This analysis showed that among patients with type 2 diabetes treated with analog insulins, the risk of developing pneumonia was 9.656 (95% CI 1,260-73,979).

The risk of death, the severity of COVID-19 and the need for dexamethasone administration did not depend on the type of hypoglycemic therapy received.

With regard to the risk of hospitalization, taking insulin or SU in patients with type 2 diabetes increased the chances of hospitalization, while the risk of hospitalization in patients taking analog insulins was higher (21,720), due to the fact that insulin was prescribed to patients with a more severe course of diabetes, a longer history of the disease (Table 3).

Table 1. Distribution of patients by clinical symptoms of COVID-19 depending on the received hypoglycemic therapy (in % of the total number of patients with diabetes)

Characteristics of the course of COVID-19	Human insulins	Analog insulins	SU	Metformin	DPP-4i	iSGLT-2
n	81	32	66	105	20	1
Loss of the sense of smell	35 (43,21%)	13 (40,63%)	30 (45,45%)	46 (43,81%)	6 (30,00)	1 (100%)
Fever	56 (69,14%)	25 (78,13%)	52 (78,79%)	83 (79,05%)	16 (80,0%)	
Cough	71 (87,65%)	30 (93,75%)	59 (89,39%)	90 (85,71%)	18 (90,0%)	
Shortness of breath	56 (69,14%)	25 (84,38%)	52 (78,79%)	79 (75,24%)	12 (60,0%)	
Chest pain	45 (55,56%)	28 (87,50%)	38 (57,58%)	69 (65,71%)	11 (55,0%)	1 (100%)
Diarrhea	11 (13,58%)	8 (25,0%)	8 (12,12%)	16 (15,24%)	5 (25,0%)	
Nausea	25 (30,86%)	15 (46,88%)	26 (39,39%)	34 (32,38%)	6 (30,0%)	
Vomiting	9 (11,11%)	3 (9,38%)	10 (15,15%)	13 (12,38%)	3 (15,0%)	
Weight loss	33 (40,74%)	17 (53,13%)	18 (27,27%)	32 (30,48%)	6 (30,0%)	1 (100%)
Headaches	70 (86,42%)	31 (96,88%)	58 (87,88%)	96 (91,43%)	18 (90,0%)	
General weakness	77 (95,06%)	32 (100,0%)	63 (95,45%)	99 (94,29%)	18 (90,0%)	
Arrhythmia	29 (35,80%)	11 (34,38%)	26 (39,39%)	39 (37,14%)	3 (15,0%)	

Table 2. Correlation analysis of the relationship between the severity of COVID-19 and hypoglycemic therapy

	Human insulins	**Analog insulins**	**SU**	**Metformin**	**DPP-4i**
Mild COVID-19 course	-0,026	-0,076	-0,063	-0,078	-0,044
Medium-severe course	0,010	0,010	0,064	0,049	-0,004
Severe COVID-19 course	0,015	0,067	-0,011	0,022	0,050
Pneumonia	0,028	0,097	0,031	0,004	0,045
Recovery	0,0001	-0,039	0,001	-0,016	-0,049
Death	-0,0002	0,039	-0,001	0,016	0,049
Hospitalization	0,136	0,154	0,062	0,058	0,099
Use of glucocorticoids	-0,032	0,019	0,014	-0,027	0,018
Loss of the sense of smell	-0,069	-0,056	-0,085	-0,080	-0,092
Fever	-0,160	-0,059	-0,098	-0,066	-0,024
Cough	0,035	0,031	-0,011	-0,012	-0,006
Shortness of breath	0,135	0,117	0,188	0,205	0,038
Chest pain	0,120	0,171	0,147	0,248	0,083
Diarrhea	-0,035	0,024	-0,062	-0,030	0,021
Nausea	-0,138	-0,050	-0,133	-0,213	-0,083
Vomiting	0,025	-0,007	0,039	-0,019	0,033
Weight loss	0,185	0,157	0,113	0,201	0,088
Headaches	-0,045	0,049	-0,061	0,027	0,010
General weakness	0,043	0,047	0,025	0,052	0,008
Arrhythmia	0,187	0,044	0,183	0,249	0,013

Table 3. The risk of hospitalization depending on previous hypoglycemic therapy among patients with diabetes in Tashkent

Group of hypoglycemic drugs	OR for hospitalisation	95% CI		p
Human insulins	3,248	1,790	5,893	<0,001*
Analog insulins	21,720	2,849	165,572	<0,01*
ПСМ	1,897	1,045	3,444	<0,05*
Metformin	0,847	0,486	1,475	0,557
DPP-4i	3,993	0,994	16,039	0,051

*p – statistically significant

For patients with type 1 diabetes, when analyzing the dependence of the severity of COVID-19 on the type of insulin received, the OR of severe course when receiving analog insulins was 19.778, 95% CI 3.385-115.562, p=0.001. For human insulins, no such results were obtained: OR 2.198, 95% CI 0.441-10.961, p=0.337.

With respect to pneumonia, the type of insulin received did not matter: the risk of pneumonia for people receiving human insulins was 3.556, 95% CI 0.916-13.808, p=0.067, for analog insulins, OR 6.667, 95% CI 0.765-58.132, p=0.086.

When analyzing the effect of certain hypoglycemic drugs, we adjusted for age and gender with the corresponding comparison groups with the calculation of the McNemar Chi-squared coefficient and OR.

Taking metformin in this analysis did not show an effect on the severity of COVID-19, the presence of pneumonia, outcomes in the form of recovery or death, the need for hospitalization and the use of dexamethasone. With regard to symptoms, persons receiving metformin in the case-control analysis with pairwise comparison more often complained of shortness of breath (OR 4,667; 95% CI 1,896-13,784, p=0,002), chest pain (OR 3,7; 95% CI 1,804-8,342; p=0,0001), more often noted arrhythmia and heartbeat sensation (OR 3.571; 95% CI 1.502-9.779, p=0.0021).

After adjusting for gender and age, persons receiving human insulins were also significantly more likely to need hospitalization: OR 2,857 (95% CI 1,161-7,997, p=0.0192). There was no difference in the severity of the course of the disease, outcomes and clinical manifestations.

Patients receiving SU, after adjusting for gender and age, significantly more often reported complaints of shortness of breath: OR 3.8 (95% CI 1.372-13.022, p=0.0066). There was no difference in the severity of the course of the disease, the need for hospitalization, taking glucocorticoids, outcomes and other clinical manifestations.

4. Discussion

Recommendations for hypoglycemic therapy of patients in the acute period of COVID-19 were mainly in cancellation

of oral preparations [1] – metformin due to the risk of lactate acidosis [2-6], iSGLT2 due to the risk of euglycemic ketoacidosis [7, 8]. However, there are data in the literature that indicate the absence of the influence of certain hypoglycemic drugs on the development of adverse outcomes in coronavirus infection in real clinical practice [9,10].

A retrospective analysis of 495 patients with type 2 diabetes out of 5473 patients with COVID-19 registered in the database of the insurance system in Korea showed no significant difference in the clinical course and outcomes of coronavirus infection depending on the oral hypoglycemic drugs taken and their combination with insulin [11].

These results were confirmed in another study conducted in the same country using multivariate logistic regression [12].

The largest-scale study of the outcomes of COVID-19 in diabetes was the CORONADO study, which included 1,317 patients. In this study, there was no effect of hypoglycemic therapy on outcomes (tracheal intubation and death). Metformin therapy before COVID-19 infection was associated with a lower frequency of deaths (HR 0.59; 95% CI 0.42-0.84), however, this advantage was leveled during multivariate analysis [13,14].

5. Conclusions

Thus, in our study, correlation analysis did not show significant links between the hypoglycemic drugs taken and the course of coronavirus infection. Patients with type 2 diabetes treated with insulin had a high risk of pneumonia (9,656, 95% CI 1,260-73,979). Patients with type 2 diabetes who received insulin or SU were more likely to need hospitalization. The risk of death, the severity of COVID-19 and the need for dexamethasone administration did not depend on the type of hypoglycemic therapy received. Treatment of patients with diabetes should be based on the current recommendations, and no matter, what glucose lowering drug is used, achieving glycemic control is key factor to prevent complications.

Limitations

We had no access to measurements of glycemia in patients with COVID-19 who were not hospitalized during acute infection, so, the impact of glycemic control is not assessed.

Strength of the Study: as far as authors are aware, it is the first study performed in the country to assess to role of glucose-lowering therapy in COVID-19 outcomes.

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Competing Interest. Authors declare no conflict of interests.

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