FACTORS INFLUENCING THE SEVERITY OF COVID-19 COURSE FOR PATIENTS WITH DIABETES MELLITUS IN TASHKENT: A RETROSPECTIVE COHORT STUDY

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***BACKGROUND*:** Since the very first outbreak, scientists have been trying to determine the most critical pathogenetic mechanisms for the development of COVID-19 and related complications, analyze individual subpopulations of patients with chronic diseases and develop optimal tactics to combat not only the infection itself but also its acute and chronic complications.
***AIM*:** to assess the COVID-19 course among patients with Type 1 and Type 2 DM.
***MATERIALS AND METHODS*:** A retrospective cohort study of Tashkent inhabitants, who had COVID-19 from April to December 2020, was performed. The data were obtained from the single electronic database of registered cases of COVID-19. All data were analyzed using a logistic regression in STATA 17.0 software. Further, the matched case-control study was performed for patients with type 2 DM and no DM based on age, gender, and BMI.
***RESULTS*:** Of the 5023 analyzed subjects, 72.63% had no diabetes mellitus (DM), 4.24% had type 1 DM, 15.19% had type 2 DM, and 7.94% was diagnosed with DM during the COVID-19 infection. DM, overweight, and obesity were associated with severe COVID-19; the most significant risk of a severe course was found in persons with type 2 DM. The risk of a lethal outcome and the need for prescription of glucocorticoids did not show a significant association with diabetes in Tashkent. The clinical features of COVID-19 were more common in patients with type 2 DM, especially for shortness of breath, chest pain, and arrhythmia. The persons receiving SU have complained of dyspnea significantly more often than matched patients without DM. Metformin and DPP4i were the groups of drugs that were not associated with significantly increased risk of hospitalization of patients because of COVID-19. The matched case-control study did not reveal statistically significant differences in the disease course severity, need for hospitalization and glucocorticoids, and death depending on the glucose-lowering therapy preceding the onset of COVID-19.
***CONCLUSION*:** Diabetes, age and overweight/obesity were associated with severe course of COVID-19 in Tashkent. There was no statistical difference in COVID-19 severity depending on initial glucose-lowering therapy.

KEYWORDS: diabetes mellitus; COVID19; metformin; insulin; complications; mortality.

COVID-19 У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ В ТАШКЕНТЕ: РЕТРОСПЕКТИВНОЕ КОГОРТНОЕ ИССЛЕДОВАНИЕ

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Обоснование. С первой вспышки ученые пытаются определить наиболее важные патогенетические механизмы развития COVID-19 и его осложнений, проанализировать отдельные субпопуляции пациентов с хроническими заболеваниями и разработать оптимальную тактику ведения не только самой инфекции, но и ее острых и хронических осложнений.
Цель. Оценить течение COVID-19 среди пациентов с сахарным диабетом (СД) 1 и 2 типов.
Материалы и методы. Проведено ретроспективное когортное исследование жителей Ташкента, перенесших COVID-19 с апреля по декабрь 2020 г. Данные были получены из единой электронной базы зарегистрированных случаев COVID-19. Данные были проанализированы при помощи одномерной и многомерной логистической регрессии с помощью программы STATA 17.0. Далее проведено исследование парных групп пациентов с СД и без СД соответствующего возраста, пола и индекса массы тела.
Результаты. Из 5023 проанализированных лиц 72,63% не имели СД, 4,24% страдали СД 1 типа, 15,19% имели СД 2 типа, у 7,94% СД был диагностирован во время COVID-19. СД, избыточный вес и ожирение были ассоциированы

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с тяжелым течением COVID-19; наибольший риск тяжелого течения был обнаружен у пациентов с СД 2 типа. Риск летального исхода и необходимость назначения глюкокортикоидов не показали значимой связи с наличием диабета у жителей Ташкента. Пациенты с СД 2 типа отмечали более выраженные жалобы, особенно на одышку, боли в грудной клетке и аритмии. Лица, получавшие препараты сульфонилмочевины, жаловались на одышку значительно чаще, чем пациенты из сопоставимой группы без СД. Метформин и ингибиторы дипептидилпептидазы 4 не были связаны со значительно повышенным риском госпитализации пациентов по причине COVID-19. Исследование парных групп не выявило статистически значимых различий в тяжести течения заболевания, необходимости госпитализации и назначения глюкокортикоидов, а также смерти в зависимости от сахароснижающей терапии, предшествовавшей возникновению COVID-19.

Заключение. Диабет, возраст и избыточный вес/ожирение были связаны с тяжелым течением COVID-19 у пациентов в Ташкенте. Статистической разницы в тяжести течения COVID-19 в зависимости от начальной глюкозоснижающей терапии выявлено не было.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет; COVID-19; метформин; инсулин; осложнения; смертность.

ABSTRACT

The pandemic caused by the SARS-CoV2 virus has not spared any country in the world. Since the very first outbreak, scientists have been trying to determine the most critical pathogenetic mechanisms for the development of COVID-19 and related complications, analyze individual subpopulations of patients with chronic diseases and develop optimal tactics to combat not only the infection itself but also its acute and chronic complications [1–3]. The role of glucose-lowering therapy preceding COVID-19 in patients with known diabetes mellitus is still unclear.

The height of the first wave of COVID-19 in Uzbekistan fell in April 2020. Since that time, all new cases of viral infection have been registered and entered into a single digital database.

Based on the COVID-19 registered cases in the capital of Uzbekistan, Tashkent, from April to December 2020, we **AIMED** to analyze the course of COVID-19 among patients with type 1 and 2 diabetes living in Tashkent, including depending on the initial glucose-lowering therapy.

AIM OF THE STUDY

To assess the COVID-19 course among patients with Type 1 and Type 2 DM.

MATERIALS AND METHODS

Site and time of the study

Study site. Tashkent city health care department electronic database, 34 Tashkent city family polyclinics.

Time of the study. Data of patients who had COVID-19 from April to December 2020 was gathered in January-March, 2021.

Study populations

5023 Tashkent inhabitants were included into the study.

Inclusion criteria: having PCR-confirmed COVID-19 from April to December 2020. Exclusion criteria: other types of pneumonia or viral diseases without confirmation of COVID-19.

Sampling method from the study population (or several sampling methods from several study populations).

Of the total population, 4 cohorts of patients were studied: 3648 people without known diabetes, 213 patients with type 1 diabetes mellitus (DM), 763 with known type 2 DM, and 399 patients with DM newly diagnosed during the COVID-19.

Study design

This was a multicenter retrospective cohort study.

Methods

The data were obtained upon request from the Tashkent city health department from a single electronic database of registered cases of COVID-19. Data registration was carried out by emergency notification by family polyclinics at patients' places of residence at the time of illness. Data on the duration of hospitalization, the severity, and disease outcomes were obtained from outpatient cards and case histories.

COVID-19 was assessed as mild in the absence of febrile and respiratory symptoms and signs of pneumonia on CT; COVID-19 was assessed as moderate in presence of fever, respiratory symptoms, and CT signs of pneumonia; and severe COVID-19 was assessed with dyspnea with rapid breathing ≥ 30 breaths/min, blood oxygen saturation ≤ 93% at rest, or arterial oxygen partial pressure (PaO2)/inhaled oxygen fraction (FiO2) ≤ 300 mmHg and pulmonary lesion on CT more than 50% developed within 24–48 hours.

Data on the received antihyperglycemic therapy, and the disease symptoms were obtained through telephone interviews after obtaining the respondents' consent to participate in the study. All data provided for further research were encrypted and depersonalized to preserve the confidentiality of information.

Statistical analysis

All data were analyzed using STATA 17.0 software. Quantitative data are shown in medians and interquartile ranges. Categorical data are shown as number of cases and in percentage of total in parenthesis.

In order to study the associations between age, weight, duration of diabetes, and existing glucose-lowering therapy and the severity of COVID-19 cases, the univariate logistic regression analysis was used.

Further, the matched case-control study was performed. Patients with type 2 DM were divided into groups based on gender, age, and BMI; for each case, patients without diabetes were identified with similar gender, age, and BMI. In total, 170 matched pairs were identified and analyzed.

Logistic regressions were used to identify odds ratios of the most common COVID-19 symptoms based on the type of diabetes.

Results are considered to be statistically significant at $p<0.05$.

Ethical expert review

Ethics committee of the Republican Specialized Scientific-and-Practical Medical Centre of Endocrinology approved the study by protocol #1 on 07.01.2021.

STUDY RESULTS

Descriptive statistics

The main characteristics of the studied groups are shown in Table 1.

In all the studied groups, women insignificantly prevailed by number. The median age of people without diabetes was 34 while the median age of people with Type 2 diabetes was 61. Persons without diabetes were overall younger; the most senior age group comprises persons with type 2 DM. Regarding the body mass index (BMI): the lowest average BMI was in the group without DM, the highest — in the group with type 2 DM. It is notable that among the dataset with type 1 DM, a relatively significant proportion of 42.72% was overweight people, and 44.13% of type 1 DM patients had obesity of varying severity. That can be indirect evidence of inadequate glycemic control and the need for revision of insulin doses. 88.86% of patients with type 2 DM and 83.71% of patients with newly diagnosed DM had excess weight or obesity.

Concerning the disease duration, most people with DM suffered from the condition from a year to ten years (both for type 1 and type 2 DM).

Patients with type 2 DM concomitant cardiovascular diseases more often: a little less than a half of patients of this group had arterial hypertension, while one-third had ischemic heart disease.

Regarding the severity of the COVID-19 course, two-thirds of the patients without DM had a mild form of infection, and only about 5% had a severe course. 47.42% of patients with type 1 DM had a mild course, while moderate and severe courses were characteristic for type 2 DM and the newly diagnosed DM patients.

The null hypothesis that the pneumonia frequency between persons with type 2 DM or newly diagnosed DM and persons with type 1 DM or no DM is equal to zero is rejected, with a Z-statistic of 25.90 and p-value of <0.0001. The difference between the pneumonia frequency of persons with type 2 DM or newly diagnosed DM and persons with type 1 DM or no DM is statistically significant at all significance levels.

We have analyzed how the age, duration of diabetes, and degree of obesity affected the severity of the COVID-19 course (Table 2).

Despite the essential age difference between groups with type 2 DM and without DM, the age is essential in aggravation of COVID-19 severity remains in all the groups, except the group of persons with type 1 DM. Duration of the DM course is vital for a severe course of COVID-19, both with type 1 and type 2 DM.

For a more detailed assessment of the influence of age and BMI on the disease course, the univariate logistic regression was used (Table 3).

Thus, increase in age of the patient has a negative impact on the possibility of the mild course of the disease, except for patients with type 1 DM; it is noteworthy that in patients without DM and patients with newly revealed DM, OR values are identical (considering different confidence intervals), while the influence of age in patients with type 2 DM is generally lower. Age has the most significant effect on the severity of the disease (1.065 for the whole sample); nevertheless, in patients with type 2 DM, this factor is almost half as high. It could be explained by the fact that in the group of patients with type 2 DM, the median age was significantly higher in comparison with the other groups, 61 years for patients with type 2 DM against 49 years for patients with type 1 DM, 47 years for patients with newly diagnosed DM, and 34 years for patients with no DM.

For BMI, a similar pattern is found with an increase in BMI in all the groups, except patients with type 1 DM, the probability of a mild course decreases, and the probability of a severe course of COVID-19 increases. In comparison with age, BMI has a more significant effect on disease severity. The role of increase in BMI in aggravating the course of COVID-19 is significant, starting from overweight: OR for overweight is 1.316 (95% of CI 1.004–1.726, p=0.047), for stage 1 obesity OR makes 3.871 (95% of CI 3.006–4.987, p<0.0001), for stage 2 obesity — 5.941 (3.968–8.895, p<0.0001) and stage 3 — 3.945 (1.322–11.734, p=0.014). However, when we analyzed the OR of overweight and obesity for the severe course of COVID-19 in patients with type 1 and type 2 DM, logistic regression did not show significant results. The possible reason is that DM (both type 1 and type 2) increases the risk of COVID-19 severity regardless of the body mass index. Indeed, the presence of DM played a significant role in the severity of COVID-19 (Table 4).

According to a matched case-control analysis with division by gender, age, and BMI among the studied groups, persons with type 2 DM needed hospitalization more often (OR 1.889; 95% of CI 1.163–3.133, p=0.0088) compared to patients without DM. While performing this study in gender groups separately, this pattern remained only in men: the relative risk of hospitalization was 2.750 (95% of CI 1.384–5.847, p=0.0025).

The matched case-control study did not reveal any statistically significant results regarding the severity of a course and outcomes.

Logistic regression for determining the factors of a severe course of COVID-19 revealed the following: among the factors that are responsible for the risk of a severe course of COVID-19, there are all types of diabetes (type 1 DM, type 2 DM, or newly revealed during the period of an acute disease course); the increased BMI (an increase in BMI by each 1 kg/m^2 showed the increased risk of a severe course of COVID-19 by 7.2%); age (the risk of a severe course of COVID-19 increased by 4.5% with every year of age); and presence of arterial hypertension (Table 5).

We analyzed the frequency of COVID-19 symptoms patients reported, depending on the presence and type of diabetes. A logistic regression was used for the analysis. Newly diagnosed diabetes was not considered in the analysis because of collinearity (Table 6).

Thus, for a group of persons without diabetes, the appearance of such clinical symptoms of COVID-19 as fever, cough, dyspnea, chest pain, diarrhea, loss of weight, headaches, and general weakness had fewer odds than in patients with diabetes.

Chances of loss of taste and sense of smell for patients with type 1 DM were higher than for patients without diabetes but lower than those with type 2 DM.

Table 1. Characteristics of the studied groups

	No diabetes (n=3648, 72.63%)	Type 1 DM (n=213, 4.24%)	Type 2 DM (n=763, 15.19%)	Newly diagnosed DM (n=399, 7.94%)
Gender, male/female	1670 (45.78%)/ 1978 (54.22%)	95 (44.60%)/ 118 (55.40%)	304 (39.84%)/ 459 (60.16%)	180 (45.11%)/ 219 (54.89%)
Median Age, years (Quartile 1–Quartile 3)	34 (27–45)	49 (39–56)	61 (54–68)	47 (36–57)
Median BMI, kg/m^2 (Quartile 1–Quartile 3)	24.80 (22.41–27.68)	28.38 (26.25–30.94)	30.12 (26.57–33.22)	28.33 (25.48–31.25)
BMI 18–24,9 (% of population by type)	44.27%	13.15%	11.14%	16.29%
BMI 25–29,9 (% of population by type)	30.78%	42.72%	25.43%	36.59%
BMI 30–34,9 (% of population by type)	11.13%	30.05%	37.75%	29.57%
BMI 35–39,9 (% of population by type)	1.78%	3.76%	9.31%	4.51%
BMI ≥40 (% of population by type)	12.04%	10.32%	16.37%	13.04%
Diabetes duration				
<1 year		-	-	
1 to 5 years		83 (38.97%)	317 (41.55%)	
5 to 10 years		92 (43.19%)	335 (43.91%)	
>10 years		38 (17.84%)	111 (14.55%)	
Concomitant cardiovascular diseases				
Arterial hypertension	321 (8.80%)	29 (13.62%)	348 (45.61%)	69 (17.29%)
IHD	134 (3.67%)	14 (6.57%)	266 (34.86%)	37 (9.27%)
COVID-19 course				
Mild (n=2848, 56,7%)	2411 (66.09%)	101 (47.42%)	185 (24.25%)	151 (37.84%)
Moderate (n=1758, 35,0%)	1059 (29.03%)	88 (41.31%)	413 (54.13%)	198 (49.62%)
Severe (n=417, 8,3%)	178 (4.88%)	24 (11.27%)	165 (21.62%)	50 (12.54%)
Pneumonia				
No	2863 (78.48%)	116 (54.46%)	241 (31.59%)	185 (46.37%)
One-sided	431 (11.81%)	55 (25.82%)	191 (25.03%)	98 (24.56%)
Two-sided	354 (9.7%)	42 (19.72%)	331 (43.38%)	116 (29.07%)
Dexamethasone use	1141 (31.28%)	110 (51.64%)	543 (71.17%)	231 (57.89%)
Died	12 (0.33%)	1 (0.47%)	13 (1.70%)	2 (0.50%)
Symptoms of COVID-19				
Loss of taste and smell	1851 (50.74%)	122 (57.28%)	452 (59.24%)	163 (40.85%)
Fever	2872 (78.73%)	186 (87.32%)	669 (87.68%)	358 (89.72%)
Cough	2505 (68.67%)	170 (79.81%)	683 (89.52%)	297 (74.44%)
Dyspnea	760 (20.83%)	60 (28.17%)	353 (46.26%)	163 (40.85%)
Chest pain	489 (13.40%)	38 (17.84%)	252 (33.03%)	114 (28.57%)
Diarrhea	503 (13.79%)	54 (25.35%)	139 (18.22%)	73 (18.30%)
Noisea	1467 (40.21%)	141 (66.20%)	474 (62.12%)	135 (33.83%)
Vomiting	177 (4.85%)	12 (5.63%)	83 (10.88%)	26 (6.52%)
Weight loss	239 (6.55%)	15 (7.04%)	112 (14.68%)	41 (10.28%)
Headache	2924 (80.15%)	190 (89.20%)	704 (92.27%)	366 (91.73%)
General Weakness	2932 (80.37%)	175 (82.16%)	708 (92.79%)	349 (87.47%)
Tachycardia, arrhythmias	213 (5.84%)	16 (7.51%)	111 (14.55%)	20 (5.01%)

Chances of appearance of characteristic symptoms of COVID-19 in patients with diabetes, generally, were higher than in patients without diabetes. Moreover, patients with type 2 DM were more prone to display these symptoms than patients with type 1 DM, which can be explained by a more complicated pathogenetic basis of type 2 DM. The patients with type 1 DM only had higher chances of appearance of nausea than patients with type 2 DM.

Influence of the medicinal therapy received by patients with DM on the course and outcome of COVID-19.

Among patients with type 2 DM receiving analog insulin, the risk of developing pneumonia was 9.562 (95% of CI 1.276-71.665, p=0.0019).

The risk of a lethal outcome, the severity of COVID-19, and the need for dexamethasone prescription did not depend on the type of the received antihyperglycemic therapy.

Table 2. Descriptive statistics of age split into DM type by columns and severity of COVID by rows and diabetes duration in patients with type 1 and type 2 DM

Severity of COVID-19	All the cases (n=5023, 100%)	no DM (n=3648, 72.63%)	Type 1 DM (n=213, 4.24%)	Type 2 DM (n=763, 15.19%)	Newly diagnosed DM (n=399, 7.94%)
Median age (Quartile 1–Quartile 3)					
Mild	34.0 (26.0–46.0)	32.0 (25.0–42.0)	49.0 (41.0–57.0)	59.0 (50.0–65.0)	44.0 (31.0–53.0)
Moderate	45.0 (34.0–58.0)	39.0 (31.0–49.0)	48.0 (34.5–56.0)	61.0 (55.0–68.0)	46.0 (37.0–57.0)
Severe	59.0 (47.0–66.0)	51.0 (38.0–61.0)	52.0 (43.0–59.5)	64.0 (58.0–71.0)	62.0 (50.0–65.0)
Median diabetes duration (Quartile 1–Quartile 3)					
Mild	-	-	6.0 (3.0–9.0)	5.0 (3.0–7.0)	-
Moderate	-	-	5.5 (3.0–9.0)	5.0 (3.0–8.0)	-
Severe	-	-	7.0 (4.5–11.5)	6.0 (3.0–10.0)	-

Table 3. Influence of age and BMI on the course of COVID-19 in patients with and without diabetes

Severity of COVID-19	All the cases (n=5023, 100%)	no DM (n=3648, 72.63%)	Type 1 DM (n=213, 4.24%)	Type 2 DM (n=763, 15.19%)	Newly diagnosed DM (n=399, 7.94%)
OR for age (95% CI)					
Mild	0.951 (0.947–0.955) p<0.0001*	0.960 (0.955–0.965) p<0.0001*	1.008 (0.985–1.031) p=0.513	0.967 (0.953–0.981) p<0.0001*	0.961 (0.947–0.976) p<0.0001*
Moderate	1.029 (1.025–1.033) p<0.0001*	1.027 (1.022–1.033) p<0.0001*	0.983 (0.960–1.005) p=0.133	1.003 (0.991–1.016) p=0.605	1.006 (0.993–1.020) p=0.362
Severe	1.065 (1.058–1.072) p<0.0001*	1.061 (1.051–1.072) p<0.0001*	1.026 (0.987–1.066) p=0.181	1.035 (1.018–1.052) p<0.0001*	1.080 (1.053–1.109) p<0.0001*
OR for BMI (95% CI)					
Mild	0.866 (0.853–0.879) p<0.0001*	0.876 (0.859–0.893) p<0.0001*	0.997 (0.926–1.074) p=0.944	0.956 (0.919–0.994) p<0.05*	0.906 (0.859–0.955) p<0.0001*
Moderate	1.099 (1.084–1.115) p<0.0001*	1.109 (1.089–1.130) p<0.0001*	0.984 (0.912–1.061) p=0.676	0.986 (0.955–1.022) p=0.471	1.050 (0.998–1.104) p=0.055
Severe	1.163 (1.136–1.191) p<0.0001*	1.154 (1.114–1.195) p<0.0001*	1.060 (0.927–1.212) p=0.391	1.080 (1.034–1.128) p<0.01*	1.112 (1.030–1.199) p<0.01*

* — statistically significant.

Table 4. The odds ratio of a severe course of COVID-19 depending on the presence of DM and its type

Factor	OR
Type 1 DM	2.127 (1.363–3.320) p=0.001
Type 2 DM	4.622 (3.716–5.748) p<0.0001

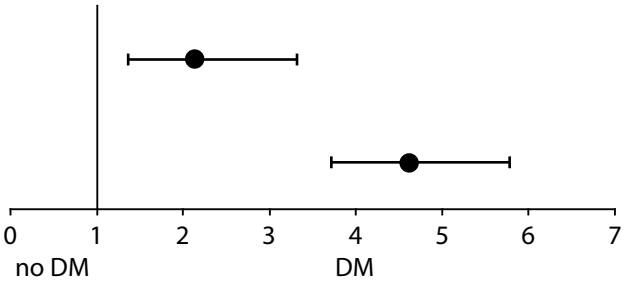
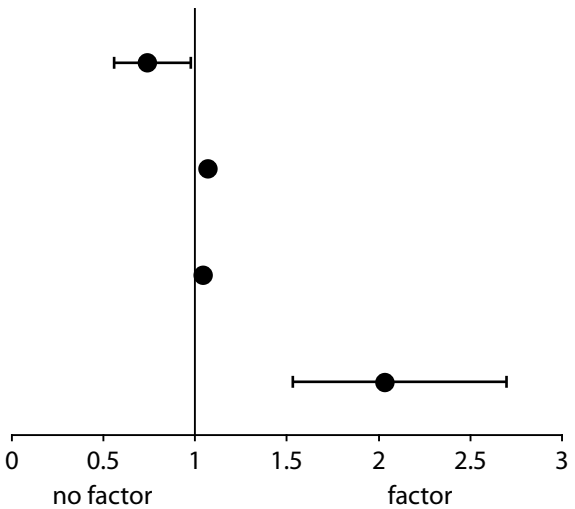


Table 5. The odds ratio of a COVID-19 severe course depending on the presence and severity of obesity and the DM presence

Factor	OR
No DM	0.737 (0.558–0.975) p=0.032
BMI, kg/m^2	1.072 (1.044–1.101) p<0.0001
Age, years	1.045 (1.035–1.055) p<0.0001
Arterial hypertension	2.036 (1.534–2.702) p<0.0001



Concerning the risk of hospitalization, the insulins or sulphonylurea (SU) therapy in patients with type 2 DM increased the chances of need for hospitalization, while OR for hospitalization of the patients taking analog insulins appeared an order of magnitude higher (21.72, 95% of CI 2.849–165.572) (Table 7).

For patients with type 1 DM, in the analysis of the dependence of COVID-19 course severity on type of the received insulin, OR of a severe course with receiving analog insulin was 21.128, SE 19.083, 95% CI 3.598–124.073, p=0.001. For human insulins, such results were not observed: OR 2.348, SE 1.931, 95% CI 0.468–11.774, p=0.300.

DISCUSSION

Representativeness of Samples

The sample is representative for the urban Uzbekistan population, based on the previous studies of diabetes epidemiology [4]. The generalizability of the study findings to the Republic population is possible taking into account the insignificantly lower prevalence of diabetes in rural areas.

Comparison with other publications

COVID-19 severety in patients with diabetes

From the earliest data that appeared in literature, the presence of DM significantly aggravated COVID-19 course severity. Thus, for example, in Wuhan, among 201 patients with confirmed COVID-19 pneumonia, there were 10.9% with diabetes. Besides, among the patients who had a history of acute respiratory distress syndrome (ARDS), DM patients were 19.0%, while among those who did not develop ARDS, DM patients made 5.1% [1].

In the Chinese research, the mortality rate was higher because of COVID-19 (16.7% against 0%, P=0.03), even given the absence of concomitant diseases among patients with DM. This research revealed that patients with DM have an emission of tissue damage enzymes, an uncontrollable inflammatory response, and hypercoagulation [5].

Another Chinese research reported high mortality among patients with DM (10.0% against 2.5%) and more frequent hospitalization to the intensive care unit (14.6% against 5.5%) in comparison with persons without DM [6].

In the English research of COVID-19 mortality, patients with DM made one-third of all people who died of COVID-19 (31.4% of the deceased were patients with type 2 DM, 1.5% were patients with type 1 DM). After adjustment for age, gender, nationality, and the region of residence, the ratio of chances of intrahospital mortality for type 1 DM amounted to 3.51 (95% of CI 3.16–3.90), for type 2 DM — 2.03 (1.97–2.09) [7].

The same authors analyzed risk factors of a lethal outcome from COVID-19 among patients with type 1 and type 2 DM of the English population. Weekly registration of lethal outcomes within 19 weeks of the analyzed period of the COVID-19 epidemic exceeded this indicator for the previous three years by 50.9% among patients with type 1 DM and by 64.3% among patients with type 2 DM. Among fatal cases of patients with DM, 62.3% occurred in persons with

cardiovascular diseases and 55.4% — in persons with eGFR lower than 60 ml/min/1.73 м^2. The factors increasing the risk of a lethal outcome for type 1 DM and 2 with COVID-19 were: male gender, advanced age, renal failure, non-Caucasian race ethnicity, a low socioeconomic status, previous history of stroke, and heart failure. In addition, in that research, a high level of HbA1c (higher than 10%) increased the risk of a lethal outcome (2.23, 95% CI 1.50–3.30, p <0.0001 for type 1 DM and 1·61; 95% CI 1.47–1.77, p <0.0001 for type 2 DM) for COVID-19.

Moreover, for type 2 DM, authors carried out a more profound analysis depending on the HbA1c level: The OR of lethal outcome was 1.22 (95% CI 1.15–1.30, p <0.0001) at HbA1c from 7.6 to 8.9% and 1.36 (95% CI 1.24–1.50, p <0.0001 at HbA1c from 9.0 to 9.9%.

Authors also showed a U-shaped dependence of mortality on BMI. The risk of a lethal outcome increased at BMI lower than 20 kg/m^2 and higher than 40 kg/m^2 (OR 2.45 (95% CI 1.60–3.75, p <0.0001) and 2.33 (95% CI 1.53–3.56, p <0.0001), for type 1 DM and 2.33 (2.11–2.56, p <0.0001) and 1.60 (1.47–1.75, p <0.0001) for type 2 DM respectively) [8].

In our research, there were no data on indicators of glycemic control. The risk of a lethal outcome and the need for prescription of glucocorticoids did not show a significant association with the presence of diabetes; however, patients with DM were more subject to a severe course of COVID-19, while the most significant risk of a severe course was found in persons with type 2 DM. Newly revealed DM was also associated with a severe course of the viral infection.

The COVID-19 course severity in our research was also associated with an increase in BMI. However, the U-shaped dependence was not noted due to our study's lack of persons with BMI lower than 18 kg/m^2.

Table 6. The frequency of COVID-19 symptoms depending on the presence of DM and its type

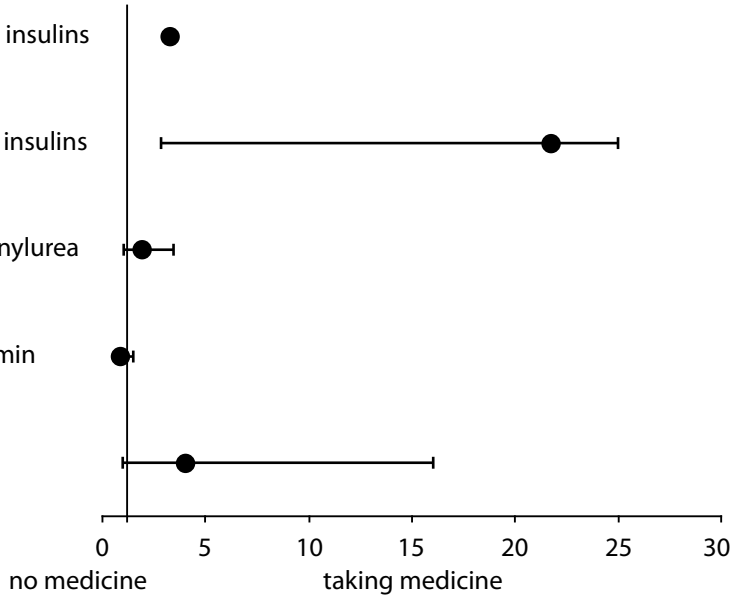
Symptom	OR (95% CI; p)		
	No DM	Type 1 DM	Type 2 DM
Loss of taste and smell p<0.0001*	1.491 (1.209–1.840) p<0.0001*	1.941 (1.386–2.719) p<0.0001*	2.104 (1.645–2.692) p<0.0001*
Fever p<0.0001*	0.424 (0.304–0.591) p<0.0001*	0.789 (0.470–1.323) p=0.369	0.815 (0.553–1.202) p=0.302
Cough p<0.0001*	0.753 (0.595–0.953) p<0.05*	1.358 (0.907–2.032) p=0.137	2.932 (2.123–4.049) p<0.0001*
Dyspnea p<0.0001*	0.381 (0.307–0.472) p<0.0001*	0.568 (0.396–0.813) p<0.01*	1.247 (0.976–1.593) p=0.078
Chest pain p<0.0001*	0.387 (0.305–0.491) p<0.0001*	0.543 (0.359–0.820) p<0.01*	1.233 (0.946–1.606) p=0.121
Diarrhea p<0.0001*	0.714 (0.545–0.936) p<0.05*	1.517 (1.017–2.262) p<0.05*	0.995 (0.727–1.361) p=0.974
Nausea p<0.0001*	1.315 (1.058–1.635) p<0.05*	3.830 (2.694–5.443) p<0.0001*	3.207 (2.488–4.134) p<0.0001*
Vomiting p<0.0001*	0.732 (0.478–1.119) p=0.150	0.857 (0.423–1.734) p=0.667	1.751 (1.107–2.769) p<0.05*
Weight loss p<0.0001*	0.612 (0.432–0.868) p<0.01*	0.662 (0.357–1.225) p=0.189	1.502 (1.027–2.197) p<0.05*
Headache p<0.0001*	0.364 (0.253–0.525) p<0.0001*	0.745 (0.425–1.305) p=0.303	1.076 (0.690–1.678) p=0.747
General Weakness p<0.0001*	0.587 (0.431–0.798) p<0.01*	0.660 (0.417–1.044) p=0.076	1.844 (1.232–2.762) p<0.01*
Tachycardia, arrhythmia p<0.0001*	1.175 (0.734–1.881) p=0.502	1.539 (0.780–3.037) p=0.214	3.226 (1.971–5.280) p<0.0001*

* — statistically significant

Table 7. OR for hospitalization in type 2 DM patients depending on the glucose-lowering therapy

Group of glucose-lowering therapy	OR for hospitalization
Human insulins	3.248 (1.790–5.593) p<0.001*
Analog insulins	21.720 (2.849–165.572) p<0.01*
Sulphonylurea	1.897 (1.045–3.444) p<0.05*
Metformin	0.847 (0.486–1.475) p=0.557
DPP4i	3.994 (0.994–16.039) p=0.051

* — statistically significant



Glucose-lowering therapy preceding COVID-19 in patients with diabetes and it's effect on COVID-19 outcomes

Since the beginning of the COVID-19 pandemic, the recommendations on antihyperglycemic therapy came down to cancellation of the tableted drugs — metformin due to the risk of a lactic acidosis development, iSGLT2 due to the risk of euglycemic ketoacidosis [9–13].

However, in actual practice, the use of any glucose-lowering drugs was not associated with the deterioration of the COVID-19 course [14].

Studies aimed to analyze the influence of the antihyperglycemic therapy preceding COVID-19 on the viral infection outcomes have already been conducted since the beginning of the pandemic.

A group of Korean scientists [15] carried out the analysis of the database of national insurance service that represents the system of social insurance of the whole country. The retrospective analysis of patients with type 2 DM was carried out from January 2019 to December 2019, depending on the received antihyperglycemic therapy. Five thousand four hundred seventy-three patients with COVID-19 were analyzed in total. The data were analyzed until an outcome — death or discharge from the hospital. Of them, 495 patients had type 2 DM. Patients with type 2 DM were older (34.5% are 70 and older than persons without DM — 8.2%); there were more male patients (56.4% against 43.4%). 18.6% of the patients received insulin, 49.1% — metformin, 34.9% — DPP4i.

On outcomes, there was no significant difference depending on the oral glucose-lowering drug and their combination with insulin (except for arterial hypertension, myocardial infarction, kidney diseases, and use of antiviral drugs and antipyretics).

Another group of Korean scientists [16] did not find any interrelation between medicamentous therapy (insulin, SU, metformin, DPP4i, iSGLT2, or RAS inhibitors) and disease severity or lethal outcomes in patients with DM and COVID-19, either. The authors used a multivariate logistic regression with adjustment by age, gender, and presence of concomitant diseases. Two hundred thirty-five patients with DM were studied.

The first prospective research of outcomes of coronavirus and diabetes (CORONADO), where 1317 patients with COVID-19 and diabetes were observed, did not reveal any influence of antihyperglycemic therapy on outcomes (a trachea intubation and lethal outcome — the primary outcome, a lethal outcome on the 7th day — the secondary outcome). In the unadjusted analysis, the authors revealed a more minor frequency of lethal outcomes among the patients taking metformin before hospitalization (OR 0.59;95%CI 0.42–0.84); however, while carrying out the multivariate analysis, a reliable difference in the outcomes was not obtained [17].

Insulin

In actual practice, among patients with DM, Cariou B et al. studied the influence of the antihyperglycemic therapy preceding COVID-19 on outcomes. Using insulin did not affect the risk of a lethal outcome [18].

In our research, using insulin — both human and analogs — did not affect the risk of lethal outcomes, although significantly increased the risk of hospitalization due to COVID-19.

Metformin

Concerning the first line of all current recommendations on DM treatments, some researchers write that they did not find any positive effects of the metformin preceding COVID-19 on the mortality or severity of the viral infection course [16, 18–21] (Table 8).

In the study by Gao Y et al. published in 2020 [22] on 110 patients with DM and COVID-19, the patients taking metformin had a higher percent of life-threatening complications (28.6% against 7,4%, p=0,004) in comparison with patients taking other glucose-lowering drugs. The infection

course severity was also higher among the patients taking metformin and higher glycemic and lactate dehydrogenase values on their admission to the hospital. In this regard, the authors recommend canceling metformin to patients upon their hospitalization with COVID-19. In our opinion, it is important to note that in the groups observed by the authors, there were more accompanying conditions — arterial hypertension and dyslipidemia. Also, there were life-threatening complications associated with the initial disease among the persons in the group receiving metformin. However, a statistically reliable difference among the groups was not found.

Nevertheless, most studies report a significant decline in mortality in the patients taking metformin, although Bramante and Jiang report a decline in mortality only among women [17, 23–28].

In mid-2020, Chinese authors from Wuhan [29] published results of a retrospective analysis of clinical data of the general Wuhan hospital where they concluded that the use of metformin by patients with type 2 DM significantly reduced the COVID-19 death rate. For insulin, acarbose, and a sulphonylurea, such reliability was not found, even though the patients taking metformin had a significantly higher level of glycated hemoglobin (9.23±2.27) compared to those not taking metformin (7.46±1.49), p=0.0032. It should be noted that in this research, only 37 patients of 131 studied were taking metformin, 26 used insulin, 22 — SU, and 38 used acarbose.

Five observation researches included in the meta-analysis [30–33] showed that with taking metformin, sepsis's mortality was significantly lower compared to those patients who did not take metformin (OR of 0.59;95% CI 0.43–0.79, p = 0.001). Observation of patients with COPD taking metformin showed that the risk of a lethal outcome in these patients was significantly lower than the patients who were not taking metformin throughout the 6.2 years of observation (HR 0.30; 95% of CI, 0.10–0.93).

A decrease in the frequency of development of ARDS in patients taking metformin as antihyperglycemic therapy before COVID-19 infection [26] is also revealed.

Cariou B. et al. [18] report that metformin use significantly reduced death probability (OR 0.38, 95%DI 0,17–0,87, p <0.0221). Mortality among the patients receiving metformin was 11%, which corresponded to overall mortality figures, whereas among the patients who were not receiving metformin, the mortality rate was 23%.

Moreover, this effect of metformin on the mortality remained after excluding from the analysis the persons with end-stage CKD and heart failure that are contraindications to prescribing metformin and did not depend on the weight or HbA1c. It follows the study results of the authors who concluded that long-term glycemic control does not influence outcomes of COVID-19 [18].

Perhaps, such effect of metformin is due to its antithrombotic [34, 35] and anti-inflammatory effect [36, 37], while in the pathogenesis of life-threatening complications of COVID-19, it is hypercoagulation and a cytokine storm that are of great importance [24].

Cheng X. et al. [27], on a cohort of 1213 patients with type 2 DM and COVID-19, showed that prolonged taking metformin was associated with a decrease in the frequency of development of heart failure (for 41%) and inflammation in COVID-19. At the same time, the authors did not find a difference concerning lethal outcomes among the patients who were and were not taking metformin. Regarding lactic acidosis, an increase in the frequency of its development in patients with a decrease in eGFR below 60 ml/min./1.73 м^2 was noted.

In our research, the use of metformin had only relative advantages because it is the only group of drugs that had no significantly increased risk of hospitalization of patients because of COVID-19. Concerning severity and outcomes of the disease, the use of metformin in our study had no advantages for patients with diabetes.

Table 8. Observation Studies of the Influence of Metformin on COVID-19 Outcomes in Diabetes.

Source	OR (95%CI)/ HR (95% CI)	Advantages of metformin use
All-cause mortality among the patients using and not using metformin		
Philipose [20]	1.39 (0.84–2.16)	no advantages
CORONADO [18]	0.59 (0.42–0.84)	no advantages
Abu_Jamous [23]	0.19 (0.05–0.70)	Advantages within 21 days after COVID-19 diagnosing
Crouse [24]	0.33 (0.13–0.84), p=0.02	Decrease in mortality by 3 times
Bramante [25]	0.76 (0.60–0.96), p=0.02	The risk of death is 24% lower
Jiang [26]	0.48 (0.13–1.74), p=0.26	no advantages
Cheng [27]	1.65 (0.71–3.86), p=0.25	no advantages
Wargny [28]	0.65 (0.45–0.93)	Reduction of risk of mortality by 33%
Risk of ARDS and HF		
Jiang [26]	0.18 (0.05–0.62), p=0.007	Reduction of ARDS risk by 84% in women
Cheng [27]	0.59 (0.41–0.83), p=0.003	41% reduction of HF

ARDS — acute respiratory distress syndrome, HF — heart failure, OR — odds ratio, HR — hazard ratio, CI — confidence interval

Sulphonylurea drugs (SU)

The structural similarity to antibiotics of a sulfonamide row allows assuming advantages of using SU in respect of bacterial pneumonia, especially it the drugs of the senior generation [38].

Dalan R. et al. [39] did not show any reliable differences in risk of mechanical ventilation or hospitalization to ICU among the patients taking SU. In our opinion, it is crucial to consider that 88% of all patients with DM in this study used metformin; therefore, it was not possible to exclude or study the role of SU alone.

The CORONADO study revealed neither the negative nor positive influence of SU on outcomes in 7 and 28 days of hospitalization [18, 28], as well as in our study.

DPP4i

Many studies aim to assess the role of DPP4i, as many works reported that coronaviruses of SARS-CoV and MERS-CoV get into a cell binding to the DPP4i enzyme [40, 41]. Therefore there were ideas that DPP4i use may enhance the risk of infection of COVID-19.

Several retrospective studies with a number of patients from 85 to 3351 did not reveal any positive or negative influence of DPP4i for COVID-19 outcomes: concerning the all-cause mortality [18, 19], mortality [16, 42], deterioration in the severity of COVID-19 [16] and need of hospitalization to ICU and trachea intubation [18, 21, 42].

Dalan R. et al. [39] reported the 4-fold increase in the risk of hospitalization to ICU among the persons taking DPP4i (OR 4.07; 1.42–11.66, p =0.009). However, the study included only 76 patients with type 2 DM, 27 taking DPP4i.

Two retrospective studies, two case series, and one prospective study (CORONADO, the final analysis) report the positive influence of DPP4i on COVID-19 outcomes — a decrease in the general mortality.

Our study did not find data on any advantages of DPP4i on severity and outcomes of COVID-19.

Clinical significance of results

Our study showed that DM, especially type 2 DM, overweight and obesity is associated with severe COVID-19, so, having early vivid clinical features of the COVID-19, patients with type 2 diabetes, overweight and obesity should by thoroughly followed up after the first signs of the viral infection. All glucose-lowering drugs except Metformin were associated with significantly increased risk of hospitalization of patients because of COVID-19. We believe that metformin should stay the first line therapy for type 2 DM.

POSITIVE SIDES OF RESEARCH.

As far as the authors are aware, this work provides the first data on the analysis of features of a course of COVID-19 among patients with type 1, type 2, and newly diagnosed DM in Uzbekistan. The study covers the significant population of the city of Tashkent representative for the whole country.

Study limitations

Data collection was carried out based on out-patient cards, extracts from clinical records, and telephone interviewing that reduces the quality of collected information and can bear subjective judgment from the interviewed patients.

Based on this sample, we could not reveal significant distinctions of influence of various drug use on severity of the disease and manifestation of symptoms.

Also, in the matched case-control analysis, we did not consider data of patients taking analog insulin and DPP4i because of the small data for the analysis.

The anthropometrical parameters used to calculate BMI (growth and weight) were also collected based on medical documentation.

In our study, there were no data on the use of GPP-1ra, and only one patient used SGLT2i; therefore, these groups of drugs were not analyzed.

Also, we had no data on glycemic control, achievement of target levels of lipids, and blood pressure that could also affect the analysis results.

Data on the existence of chronic complications of DM in groups of patients with type 1 and type 2 DM were missing.

CONCLUSION

Thus, DM, overweight and obesity was associated with severe COVID-19, the most significant risk of a severe course was found in persons with type 2 DM. The risk of a lethal outcome and the need for prescription of glucocorticoids did not show a significant association with the presence of diabetes in Tashkent. The clinical features of COVID-19 were more pronounced in patients with type 2 DM, especially for shortness of breath, chest pain, and arrhythmia. The persons receiving SU have complained of a dyspnea significantly more often than matched patients without DM. Metformin was the only group of drugs that was not associated with significantly increased risk of hospitalization of patients because of COVID-19. The matched case-control study did not reveal statistically significant differences in the disease course severity, need for hospitalization and glucocorticoids, and death depending on the glucose-lowering therapy preceding the onset of COVID-19.

Diabetes, age, and overweight/obesity were associated with severe course of COVID-19 in Tashkent. There was no statistical difference in COVID-19 severity depending on preceding glucose lowering therapy, while metformin and DPP4i were the groups of drugs that were not associated with significantly increased risk of hospitalization of patients because of COVID-19.

ADDITIONAL INFORMATION

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All authors approved the final version of the article before publication, agreed to be responsible for all aspects of the work, implying proper study and resolution of issues related to the accuracy or conscientiousness of any part of the work.

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