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Effects of Metformin, Insulin on Hematological Parameters of COVID-19 Patients with Type 2 Diabetes

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ABSTRACT

Background: COVID-19 infection caused by SARS-CoV-2 can result in multi-organ injuries and significant mortality in severe and critical patients, particularly those with type 2 diabetes as a comorbidity. Metformin and insulin are the main diabetes medications that affect the outcome of patients with COVID-19. **Objective:** The purpose of our study was to find out the features of the hematological indicators of patients with COVID-19 patients and type 2 diabetes. **Methods:** This is a retrospective study of the hospital confirmed COVID-19 patients between January to March 2022, who were admitted to Transcarpathian Regional Clinical Infectious Diseases Hospital (Uzhhorod, Ukraine). **Results:** The effect of type 2 diabetes, metformin, and insulin on COVID-19 were analyzed, respectively. Demographics and blood laboratory indices were collected. In patients who took metformin, the level of CRP was significantly lower than in patients who did not take metformin (24 mg/L [IQR 15 - 58] vs 52 mg/L, [IQR 22–121], P = 0.046). **Conclusion:** Our findings suggest that pre-admission metformin use may benefit COVID-19 patients with type 2 diabetes.

Keywords: COVID-19, diabetes, metformin, insulin.

1. BACKGROUND

Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first reported in December 2019 (1, 2). The severity of COVID-19 ranges from asymptomatic to severe infection leading to death (1).

Diabetes is a chronic disease that affects over 463 million people around the world (3). Studies reported that 20–50% of COVID-19 patients have diabetes depending on different areas (4). Also diabetic patients with COVID-19 had poorer prognosis compared to non-diabetic patients (5-7).

The diabetes medication regimen may have influenced the progression (8, 9). The most commonly used diabetes medications are metformin and insulin. Theoretical evidence suggests that metformin may be beneficial for reducing proinflammatory and profibrotic states (2, 10, 11) and improving immune response (12). Insulin treatment may increase the risk of poor prognosis by increasing renal Angiotensin Converting Enzyme 2 (ACE2) expression in diabetic mice (13).

2. OBJECTIVE

In this study, we sought to perform a retrospective analysis of metformin and insulin effects in COVID-19 patients with Type 2 Diabetes Mellitus (T2DM).

3. MATERIAL AND METHODS

Ethical Approval of the Study Protocol

This was a retrospective study conducted at the Transcarpathian Regional Clinical Infectious Diseases Hospital (Uzhhorod, Ukraine). The study protocol was approved by the Ethics Committees of Transcarpathian Regional Clinical Infectious Hospital.

Study Design and Participants

We used retrospective patient data collected from medical records available from the e-health information system, which included all adult patients

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(≥18 years old) admitted from January 2021 to March 2022 with a Polymerase Chain Reaction (PCR) confirming diagnosis of SARS-CoV-2 infection using nasal swabs.

In-hospital confirmed COVID-19 patients were divided into T2DM and non-diabetes. T2DM was defined by fasting venous or capillary glucose ≥ 7.0 mmol/L; two-hour postprandial venous plasma glucose or random plasma glucose ≥ 11.1 mmol/L according to the World Health Organization diagnostic criteria (14). A study flow diagram is shown in Figure 1.

Data Collection

Demographics, comorbidities, laboratory tests, treatments of COVID-19 patients with and without T2DM were collected from the Electronic Medical Records (EMR).

Statistical Analysis

The results are reported as the median (interquartile range [IQR]) for non-normal continuous variables and number [percentage] for categorical variables. The classification variable was represented as a count (%). Differences in parameters among groups were analysed using the Student’s t-test for variables with a normal distribution. The Mann–Whitney U-test was

| Characteristics | Normal range | Non-diabetes (N = 65) | T2DM (N = 80) | P-value |
|------------------------------|--------------------------------|-----------------------|---------------|---------|
| Age (years) | - | 53.66 ± 13.37 | 67.00 ± 7.70 | <0.001 |
| Male (n, %) | - | 46.10 % | 45.00 % | 0.459 |
| Comorbidities (n, %) | | | | |
| Hypertension | - | 8 (12.3 %) | 36 (45 %) | <0.001 |
| Cardiovascular disease | - | 27 (41.5 %) | 66 (82.5 %) | 0.015 |
| Chronic kidney disease | - | 8 (12.3 %) | 28 (35 %) | 0.017 |
| Severity categories (n, %) | | | | |
| Mild | - | - | - | - |
| Moderate | - | 60 (92.3 %) | 44 (55 %) | - |
| Severe | - | 4 (6.2 %) | 12 (15 %) | - |
| Critical | - | 1 (1.5 %) | 24 (30 %) | - |
| Baseline laboratory indices | | | | |
| Blood glucose | 3.90–5.6 mmol/L | 5 (4-6) | 12 (-15) | < 0.001 |
| White blood cells | 3.50–9.50 × 10 ⁹ /L | 7 (5-10) | 9 (6-12) | 0.139 |
| Lymphocytes | 1.10–3.20 × 10 ⁹ /L | 1 (1-1) | 1 (1-2) | 0.647 |
| Monocytes | 0.12–1.20 × 10 ⁹ /L | 0 (0-0) | 0 (0-0) | 0.651 |
| Neutrophils | 1.80–6.30 × 10 ⁹ /L | 6 (4-8) | 8 (5-10) | 0.100 |
| Creatinine | 57.00–97.00 μmol/L | 106 (87-119) | 102 (84-124) | 0.647 |
| CRP | 0–8.00 mg/L | 50 (13-120) | 28 (20-72) | 0.553 |
| D-dimer | 0–0.55 μg/mL | 1 (0-2) | 2 (1-3) | 0.013 |
| PCT | <0.10 ng/mL | 0 (0-0) | 0 (0-1) | 0.129 |
| COVID-19 treatment protocols | | | | |
| Antibiotics (n, %) | - | 29 (44.6 %) | 52 (65 %) | 0.328 |

Table 1. Characteristics of baseline laboratory indices of patients with or without T2DM in COVID-19 cases

employed for continuous variables with a non-normal distribution, and the χ² test was used for categorical variables. A predictive model based on logistic regression was developed to predict the presence of metformin treatment based on significant laboratory parameters. All statistical analyses were performed using SPSS. P value ≤0.05 was considered to indicate statistical significance

4. RESULTS

Demographic characteristics of the study population

Among the 145 confirmed patients, the median age was 62.66 ± 12.96, 66 patients (45.5%) were male.

Patients with T2DM were older than patients without T2DM 53.66 ± 13.37 vs 67.00 ± 7.70 (P = <0.001). Among these 80 patients with diabetes, 100% are T2DM. At hospital admission, the distribution of severity category was: 92.3% vs 55% moderate, 6.2% vs 15% severe, and 1.5% vs 30% critical COVID-19 patients without or with TD2M, respectively.

Most of the hematological indicators, such as the level of white blood cells (P=0.139), lymphocytes (P=0.647), monocytes (P=0.651), neutrophils (P=0.100), creatinine (P=0.647), CRP (P=0.553) and procalcitonin (P=0.129) did not differ significantly in the 2 groups of patients (with or without T2DM). The level of d-dimer was higher in patients who had comorbid pathology - TD2M (P=0.013). Hematological

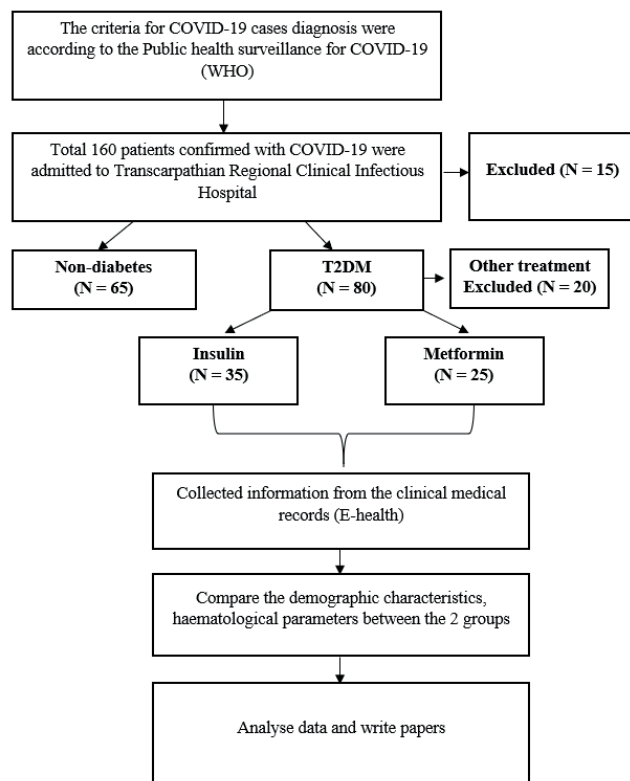


Figure 1. Study flow diagram

| Characteristics | Non-metformin (N =16) | Metformin (N =25) | P-value | Non-insulin (N = 10) | Insulin (N = 35) | P-value |
|------------------------------|-----------------------|-------------------|---------|----------------------|------------------|---------|
| Concentrations (per day) | - | 1 (0.55 – 1.52) | NA | - | 35 (28.2 – 50.3) | NA |
| Age (years) | 58.67 ± 10.81 | 60.80 ± 12.56 | 0.518 | 52.67 ± 8.81 | 67.8 ± 9.26 | 0.038 |
| Gender (M, %) | 7 (43.7 %) | 12 (48 %) | 0.657 | 6 (60 %) | 17 (48.5 %) | |
| Comorbidities (n, %) | | | | | | |
| Hypertension | 7 (43.7%) | 7 (28 %) | 0.257 | 3 (30 %) | 9 (25.7%) | 0.436 |
| Cardiovascular disease | 2 (12.5%) | 4 (16 %) | 0.368 | 1 (10%) | 5 (14.2 %) | 0.813 |
| Chronic kidney disease | 7 (43.7 %) | 7 (28 %) | 0.537 | 4 (40 %) | 10 (28.5%) | 0.251 |
| Baseline laboratory indices | | | | | | |
| Blood glucose | 7 (5-14) | 10 (8-14) | 0.014 | 5 (4-8) | 14 (9-15) | < 0.001 |
| White blood cells | 8 (6-12) | 9 (6-10) | 0.463 | 7 (5-11) | 9 (7-12) | 0.082 |
| Lymphocytes | 1 (1-1) | 1 (1-1) | 0.666 | 1 (1-2) | 1 (1-1) | 0.430 |
| Monocytes | 0 (0-0) | 0 (0-0) | 0.040 | 0 (0-0) | 0 (0-0) | 0.368 |
| Neutrophils | 7 (5-11) | 7 (4-9) | 0.315 | 6 (4-8) | 9 (6–11) | 0.022 |
| Creatinine | 102 (86-119) | 105 (90-124) | 0.644 | 102 (86-118) | 102 (87-127) | 0.647 |
| CRP | 52 (22-121) | 24 (15-58) | 0.046 | 40 (16-104) | 43 (18-100) | 0.846 |
| D-dimer | 1 (0-3) | 1 (0-3) | 0.544 | 1 (0-3) | 2 (1-3) | 0.181 |
| PCT | 0 (0-1) | 0 (0-1) | 0.660 | 0 (0-1) | 0 (0-1) | 0.340 |
| COVID-19 treatment protocols | | | | | | |
| Antibiotics (n, %) | 13 (81.2 %) | 14 (56 %) | 0.486 | 8 (80%) | 25 (71.4%) | 0.587 |

Table 2. Characteristics of baseline laboratory indices in metformin or insulin users.

parameters of COVID-19 patients with type 2 diabetes depending on insulin or metformin treatment.

During hospitalization, 25 cases with T2DM had metformin. Patients had in-hospital metformin with a median of 1.0 g per day [IQR 0.55–1.52]. In patients who took metformin, the level of CRP was significantly lower than in patients who did not take metformin (24 mg/L [IQR 15 - 58] vs 52 mg/L, [IQR 22–121], P = 0.046) (Table 2, Figure 2).

35 patients had insulin after admission. In-hospital insulin users with a median of 35.0 unit per day [IQR 28.2 - 50.3]. Higher blood glucose levels (14 mmol/L, [IQR 9 –15] vs. 5 mmol/L [IQR 4 –8], P = < 0.001) were seen in insulin users. Patients in the insulin group had higher WBC (9 × 10⁹/L, [IQR 7 –12] vs. 7 × 10⁹/L [IQR 5 –11], P = 0.082) and neutrophils levels than those of the non-insulin group (9 × 10⁹/L, [IQR 6 –11] vs. 6 × 10⁹/L [IQR 4–8], P = 0.022) with no difference in general characteristics and other laboratory indices.

5. DISCUSSION

This retrospective study is aiming to explore the effects of metformin and insulin on hematological parameters in patients with COVID-19 and T2DM. We validated the risk of T2DM in COVID-19 patients. Patients with T2DM had poorer prognosis (ICU admission and more patients were severe and critically) compared to non-diabetic patients. In terms of mortality from COVID-19 in patients with diabetes, several lines of evidence suggest that diabetes is one of the major causes of

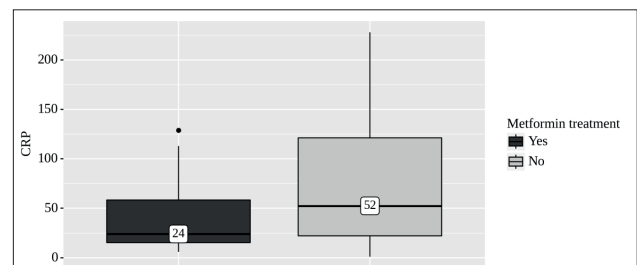


Figure 2. Analysis of CRP conditioning on Metformin treatment

death in COVID-19 patients (7, 15). The negative effects of COVID-19 are thought to be caused by microvascular disease, endothelial dysfunction, severe pneumonia, and inflammatory storm (16). Older age and high CRP were thought to be factors contributing to the high mortality rate from COVID-19 in diabetic patients (17).

Metformin is the marketplace leader among glucose-lowering agents for the management of T2DM. In recent years, metformin has attracted attention again for its antiviral effect and anti-inflammatory activity that may help in reducing the risk of severe COVID-19 beyond the effects of glucose control (11, 12, 18).

Additionally, it has been discovered that metformin is linked to a significantly lower mortality rate in people with respiratory pathologies like a chronic obstructive pulmonary disease (19). In our study, a decrease in CRP was observed when using metformin. These findings suggest that metformin use prior to admission may have protective effects for COVID-19 patients with T2DM.

Regarding the COVID-19 in diabetic patients who used insulin, a lot of studies implied an increased risk of mortality in confirmed COVID-19 cases with pre-admission insulin treatment (17, 20-22). We found in-hospital insulin usage was closely associated with higher levels of WBC and neutrophils which indicates deteriorated inflammation.

6. CONCLUSION

In this study, we found that COVID-19 patients with T2DM experienced negative outcomes, which may have been caused by worsening inflammation. Metformin use prior to admission was linked to declining CRP levels among COVID-19 patients with T2DM. In the long run, metformin may be more advantageous than insulin for COVID-19 patients with T2DM. To confirm the current findings, more research is required.

- **Ethical Approval:** This experiment was approved by the ethics committee of Transcarpathian Regional Clinical Infectious Hospital. The data are de-identified; therefore, the requirement of written informed consent was waived. The study was conducted in compliance with the Declaration of Helsinki principles for ethical research.
- **Author's contribution:** All authors were involved in all steps of preparation of this article. Final proofreading was made by the first author.
- **Conflicts of interest:** There are no conflicts of interest.
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