Diabetes - a Consequence of COVID-19 Infection

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**ABSTRACT**

**Background:** COVID-19 infection has shown many complications on all organ systems, including the pancreas, during the acute phase of infection and in the post covid period. **Objective:** Our goal was to compare the frequency of patients with type 1 and type 2 diabetes in the Outpatient Clinic "Srce Sarajevo", in the year before COVID-19, 2019, and during the COVID-19 infection, in 2020 and 2021. Our second goal was to monitor the incidence of diabetes after COVID-19 infection, the time of onset after the acute phase of the disease, and treatment options for individual patients depending on the value of glucose. **Methods:** The study was designed as a retrospective-prospective, with the consent of the Director of the Outpatient Clinic "Srce Sarajevo", and patient consent, in the period of January 2019 to December 2021. The study included 371 patients at the age between 18-70. **Results:** In 2020 and 2021 there was a significant difference in the number of patient diagnosed with diabetes who came for examination, compared to 2019. The number of new-onset diagnosed patients with type 1 and type 2 diabetes was significantly higher in 2020 and 2021 compared to 2019. In 2020, out of five newly discovered type 1, 3 of them, with an average age of 23 (+/- 1-4), overcame COVID-19 infection, and diabetes was detected 3-4 weeks after overcoming COVID-19 infection. Of the 122 type 2 patients, 19 were newly diagnosed, 47 were of average age (+/- 2-6), 13 were COVID-19 infected, and diabetes was detected 4-6 weeks after infection. In 2021, out of 4 newly discovered type 1, 3 of them, with an average age of 22 (+/- 1-2), overcame COVID-19 infection, and diabetes was detected 2-3 weeks after overcoming COVID-19 infection. Of the 114 type 2 patients, 32 were newly diagnosed, 45 were of average age (+/- 2-6), 23 were COVID-19 infected, and diabetes was detected 6-8 weeks after infection. **Conclusion:** COVID-19 infection adversely affects the pancreatic tissue leading to the clinical picture of type 1 and type 2 diabetes, and all patients, especially those at high risk of developing the disease suggest blood sugar testing, 3-4 weeks after the acute phase of the disease, and earlier if they were on corticosteroid therapy.

**Keywords:** Diabetes mellitus type 1 and type 2, COVID-19 infection, treatment.

1. **BACKGROUND**

Coronavirus disease 2019 (COVID-19) is a viral disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was officially confirmed during December 2019 in the city of Wuhan, Hubei Province, China, while the first case of the disease was recorded on November 17, 2019 (1). According to the World Health Organization (WHO), by 2 February 2022, there have been 380,321,615 confirmed cases of COVID-19, including 5,680,741 deaths (2).

Since the beginning of the pandemic, many studies have been done that have examined comorbidities associated with COVID-19. Comorbidities such as hypertension, obesity, heart disease, and diabetes mellitus are most common in people with severe COVID-19 outcomes (3, 4). Furthermore, a large number of people who had COVID-19 infection developed hyperglycemia, whether they were previously diagnosed with diabetes or those with new-onset diabetes (5, 6, 7). Also, it remains unclear whether new-onset diabetes occurs by the same mechanisms as type 1 and type 2 diabetes, or whether new-onset diabetes is an atypical form of diabetes (8).

The exact mechanism of how new-onset diabetes develops after COVID-19 is not yet known, but it is assumed that there are several mechanisms that explain the increase in the incidence of new-onset diabetes in patients with COVID-19. One of the proposed mechanisms is...
that SARS-CoV-2 binds to receptors of the enzyme that converts angiotensin-2 (ACE-2) expressed on adipose tissue, lungs, small intestine, kidneys, and pancreas. After virus endocytosis, ACE-2 decreases, leading to overexpression of angiotensin II, which may interfere with insulin secretion (9-12).

2. OBJECTIVES
In this study our goal was to compare the frequency of patients with type 1 and type 2 diabetes in the Outpatient Clinic "Srce Sarajevo", in the year before COVID-19, in 2019, during COVID-19 in 2020 and 2021. Our second goal was to monitor the incidence of diabetes after COVID-19, the time of onset after the acute phase of the disease, and treatment options for individual patients depending on the value of glucose.

3. PATIENTS AND METHODS

Participants
The study was designed as a retrospective-prospective, and was conducted at the Outpatients Clinic "Srce Sarajevo", with the consent of the Director of the Polyclinic and patient consent, in the period January 2019 to December 2021. The study included 371 patients aged 18-70. The number of patients with type 1 diabetes was 47 in three years, and the number of patients with type 2 diabetes was 524 who responded to the examination.

Procedure
All subjects, 371 of them, had blood taken from the cubital vein, according to the standard blood draw procedure, on an empty stomach (without any therapy before blood draw) at the Outpatient Clinic "Srce Sarajevo". Fasting glucose (FG) values were determined, glucose two hours after a standard meal and quarterly average glycemia - HbA1C.

Research methods
After the results were obtained, the doctor talked to the patients, examined them, interpreted the findings and determined the therapy. From the anamnesis, we extracted data on the duration of diabetes and therapy for diabetes. For newly discovered cases in 2020 and 2021 we asked if they had a COVID-19 infection. For those who overcame COVID-19 infection, we examined what time period elapsed from overcoming the infection to diagnosing diabetes. We were also interested in whether they received corticosteroids during COVID-19 infection.

Statistical analysis
SPSS17.0 for Windows statistical program was used to create statistical calculations. Arithmetic mean, standard deviation, percentage and t-test were used, also.

4. RESULTS

In the Outpatient Clinic "Srce Sarajevo", for 2019 we extracted the data for 96 patients, age range 18-70. Among them, there were eight patients diagnosed with type 1 diabetes, and one patient diagnosed with new-onset type 1 diabetes. There were 88 patients diagnosed with type 2 diabetes, and six patients with new-onset type 2 diabetes. Out of total number of eight patients with type 1 disease seven patients were already diagnosed, from which five men and two women, all on insulin therapy, basal-bolus regimen, and one newly discovered man, with administered insulin therapy, basal-bolus regimen. In the type 2 cohort, 88 patients were examined, 82 patients with earlier established diagnosis, and six newly diagnosed, with an average age of 57 (±2-12) years. From the total number in type 2 patients group, 64% were receiving oral hypoglycemic therapy, 8% a combination of GLP-1 RA and oral hypoglycemia, and 28% were on regular insulin therapy. The group of six recently diagnosed Type 2 diabetics received oral hypoglycemic in therapy. Patient Type 1, newly diagnosed, had GUK values at 14.5 mmol/l, 2 h after a standard meal of 18.1 mmol/l, and HbA1C was 7.8%. The values in newly diagnosed cohort of 6 patients with Type 2, the mean fasting GUK was 13.6 (±2.4-5.6) mmol/l, the postprandial GUK value was 15.6 (±1.5 -4.7) mmol/l, and the average HbA1C was 12.4 (±1.1-2.1) %.

In 2020 in this clinical setting there were a total number of 145 patients with diabetes, with type 1 there were 21 patients, with new-onset 5 patients, and type2 122 patients, with additional diagnosis of 19 patients. In the cohort of 5 new-onset patients with type 1 diabetes, 3 patients, with an average age of 23 (±1-4), recovered from COVID-19 infection, and diabetes was detected 3-4 weeks after recovering from COVID-19 infection. Also, they were administered a corticosteroid therapy. The average values of FBG were 15.5 (±2.3-5.4) mmol/l, glucose after meals 16.2 (±1.5-3.4) mmol/l, and average HbA1C value was 7.3 (±0.4-0.9) %. All patients were regularly receiving insulin therapy, basal-bolus regimen. Out of the total number of 122 type 2 patients, 19 were new-onset, with mean age 47 (±2-6), from which 13 recovered from COVID-19 infection, and were not administered corticosteroid therapy. The diabetes was detected 4-6 weeks after COVID-19 infection. The average values of FBG were 10.5 (±1.3-2.4) mmol/l, glucose after meals 12.2 (±1.5-2.3) mmol/l, and HbA1C was 7.6 (±0.4-0.9) %. All of 13 patients received oral hypoglycemics in therapy.

In the 2021, the total number of patients with diabetes was 152, from which 18 type 1 diabete, and new-onset 4, while with type 2 there was a record for 114 patients, and 32 of them were examined. Out of four new-onset type 1, three of them, average age 22 (±1-2), recovered from the COVID-19 infection. Also, diabetes was detected 2-3 weeks after recovering from COVID-19 infection and they were not administered corticosteroids. The average values of FBG were 12.1 (±2.1-2.6) mmol/l, glucose after meals 14.1 (±1.5-2.4) mmol/l, and HbA1C was 7.1 (±0.4-0.9) %. All patients were receiving insulin therapy, basal-bolus regimen. Of the 114 type 2 patients, 32 were newly diagnosed, 45 were of average age (±2-6), and of them 23 were recovered from COVID-19 infection. Also, diabetes was detected 6-8 weeks after COVID-19 infection. Out of 23 patients, three of them were on corticotherapy, and 19 were not receiving corticotherapy. The average values of FBG were 9.5 (±1.1-2.9) mmol/l, glucose after meals 11.6 (±0.9-2.3) mmol/l, and HbA1C was 7.5 (±0.4-1.1) %. The three patients who underwent corticotherapy received insulin premix in two doses. Moreover out of 19 patients 15 received one hypoglycemic therapy and four patients received two oral hypoglycemic agents immediately.
In 2020 and 2021 we recorded a significantly larger difference in the number of patients diagnosed with diabetes who presented for examination, compared to 2019, p < 0.01. One of the reasons is the epidemiological situation itself and the reduced number of visits to public health institutions. The number of newly diagnosed patients with type 1 and type 2 diabetes was significantly higher in 2020 and 2021 compared to 2019, p < 0.01. There was a significant number of new-onset type 1 and type 2 patients after recovering from COVID-19 infection compared to new-onset cases without covid infection. Moreover, the value of P < 0.01. Therapy did not differ significantly for type 1 diabetes in 2019, 2020, 2021, as well as for those with new-onset post-covid syndrome and those without COVID-19, all were on a basal-bolus regimen with an average international units (IU) number in 2019 54 (+/- 4-8) IU, in 2020 56 (+/- 2-6), in 2021 55 (+/- 2-6), p = 0.02. The values of FPG and glucose after meals, as well as HbA1C were lower in new-onset cases in 2020 and 2021, compared to 2019 p < 0.02. The most common reported symptoms of polydipsia, polyphagia, polyuria were reported, and no recently diagnosed patients had ketonuria or ketoacidosis. Initial therapy for type 2 diabetes did not differ significantly in new-onset cases with COVID-19 infection compared with treatment in new-onset patients without COVID-19 infection, P = 0.02, except for two patients with postcovid diabetes who received corticotherapy and whose glycemia required insulin therapy. The values of FPG and postprandial glucose, as well as HbA1C were lower in new-onset cases in 2020 and 2021, compared to 2019 p < 0.002. Also, most likely patients with the first symptoms of polydipsia, polyphagia, polyuria reported for examination, and also because of the suggestion to control sugar after covid infection. HbA1C levels in 2020 and 2021 was on average lower than in 2019, P < 0.002, and suggested that diabetes did not last for a long time and they could be associated with COVID-19 infection. The average life expectancy of type 2 patients in 2020 and 2021 was lower than in 2019, p < 0.001.

5. DISCUSSION

Due to the COVID-19 pandemic, a number of new-onset diabetes has also emerged. Patients diagnosed with diabetes are at higher risk of unregulated glycemia, complications of diabetes, as well as the occurrence of acute conditions such as ketoacidosis and hyperglycemic hyperosmolar condition. Questions are asked "what is the exact mechanism of diabetes after COVID-19 infection", "whether new-onset diabetes occurs in patients with type 1 and type 2 diabetes", "with the occurrence of hyperglycemia after COVID-19 infection whether changes the natural history of the disease ". Through our study, we tried to bring closer the answers to these questions in order to better manage new-onset diabetes in patients who have experienced COVID-19. Also, our study is the first in Bosnia and Herzegovina to address this issue.

Several studies have shown that patients with diabetes are at high risk of hospitalization, also at risk of severe forms of COVID-19, and it has been suggested that glycemia should be measured during hospitalization regardless of whether diabetes has been previously diagnosed (15-16). Furthermore, several studies showed that ketoacidosis may occur as a complication in patients with new-onset diabetes (10, 17, 18). That the percentage of people with diabetes increased in the COVID-19 pandemic is also shown by the meta-analysis Boddu et all, which is in line with our data (19).

Furthermore, in our study, not many patients used corticosteroid therapy, so we cannot say with certainty whether the use of corticosteroid therapy alone led to worsening diabetes or was the cause of new-onset diabetes. On the other hand, a study by Zhou et all included a sufficient number of patients linking the use of corticosteroid therapy with new-onset diabetes (20). Interestingly, in the randomized RECOVERY study, which examined the use of corticosteroid therapy in hospitalized patients with COVID-19, only 4 had sequelae of corticosteroid use, two of which were hyperglycemia (21).

Our study also showed that the number of new-onset type 1 diabetes is growing compared to 2019. A study by Marchand et all found that Type 1 diabetes onset triggered by COVID-19 (22). In our study, we also examined FPG, HbA1C as a predictor of new-onset diabetes. Studies by Yang et all and Wang et all have shown that FPG and HbA1C are good predictors of prognosis in COVID-19 infection (23, 24).

As for therapeutic procedures, most of our patients received insulin therapy. A study by Sardu et all showed that in hospitalized patients insulin infusion may be an effective method for achieving glycemic targets and improving outcomes in patients with COVID-19 (25). So far, there have been no studies that examine which drug is most suitable for new-onset diabetes after COVID-19.

This study has several benefits, primarily one of the first studies showing the number of new-onset diabetes in Bosnia and Herzegovina, both in patients with type 1 diabetes and in patients with type 2 diabetes. Also, all data, such as BMI, HbA1C, FBG as well as other metabolic parameters were analyzed in detail in the study. However, this study also has a limitation, because it shows the number of patients who have new-onset diabetes from one medical institution, while we do not have data on the number of new-onset diabetes from other medical institutions.

6. CONCLUSION

Based on a retrospective-prospective study that we conducted over three years at the Outpatient Clinic "Srce Sarajevo", we came to the following conclusions: In 2020 and 2021 the total number of patients with type 1 and type 2 diabetes was higher than in 2019. New-onset diabetes was significantly more common than in newly diagnosed cases of diabetes without COVID-19 infection. The average dose of insulin therapy for type 1 diabetes did not differ significantly in new-onset diabetes compared to insulin doses in patients who did not have COVID-19 infection. Therapy for type 2 diabetes did not differ significantly between new-onset type 2 diabetes after COVID-19 and in patients who did not have COVID-19 infection. The time after COVID-19 and the diagnosis of new-onset diabetes averaged 5-4 weeks for type 1 and 4-6 weeks for type 2 diabetes. Following our research, we suggested that all patients with COVID-19 infection should be monitored for postprandial blood sugar,
especially type 2 diabetes, who are at high risk for diabetes (age, heredity, obesity, hypertension, hyperlipidemia, and other endocrine disorders).

- **Patient Consent Form:** All participants were informed about subject of the study.
- **Author’s Contribution:** A.B. and A.D. gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. D.R. had a part in article preparing for drafting or revising it critically for important intellectual content. Z.V.A. gave final approval of the original research and made substantial contribution in monitoring of the data compilation and evaluation of results.
- **Conflicts of interest:** There are no conflicts of interest.
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