Long-term Effects of Covid-19 İnfection and Pandemic Period in Patients with Type 2 Diabetes Mellitus

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Article

Long-term Effects of Covid-19 İnfection and Pandemic Period in Patients with Type 2 Diabetes Mellitus

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Abstract: Objectives: Our study aimed to investigate the effect of Covid-19 infection and the pandemic period on diabetes regulation and other metabolic parameters in patients with type 2 diabetes mellitus. **Methods**: Two groups of patients who were selected from patients who were admitted to internal medicine or endocrinology and metabolism outpatient clinics between 01/02/2021 - 01/05/2021, received inpatient treatment due to COVID-19 and did not have COVID-19 infection during the pandemic period were established. A total of 127 patients, 79 of whom were women and 64 of whom had Covid-19, were included in the study. The changes in control diabetes and other metabolic parameters of the patients after six months were compared as inter- and intra-group, and the differences between the groups were examined. **Results**: A statistically significant decrease was detected between the HbA1c measured before the pandemic and at control in all patients ($p<0.05$). A significant increase was detected in LDL, HDL, and Total cholesterol values ($p<0.05$). In the patient group with COVID-19, HbA1c was detected to be significantly lower between before and after the disease, and there was a statistically significant increase in Total cholesterol, LDL, and HDL values ($p<0.05$). In the patient group who did not have COVID-19, HbA1c was significantly lower between the pre-pandemic and control, and no significant difference was detected in other parameters. **Conclusions**: In our study, we determined that COVID-19 infection did not disrupt diabetes regulation in diabetic patients but caused dyslipidemia by increasing cholesterol levels. Dyslipidemia is predicted to increase atherosclerotic complications.

Keywords: Type 2 diabetes mellitus; Covid-19; pandemic

1. Introduction

Covid19 is a disease caused by the SARS-CoV2 virus, a new member of the coronavirus family. It was first detected in Wuhan in 2019, then spread worldwide and caused a pandemic [1]. It has a more severe course and higher mortality in patients who are elderly and have comorbid diseases such as diabetes. COVID-19 patients with diabetes have a higher rate of hospital admission, hospitalization, development of severe pneumonia, and mortality [2]. The main reasons for the more severe course of infectious diseases in diabetic patients include chronic inflammation, a tendency to cellular attachment, impaired T lymphocyte cell functions, decreased virus clearance, uncontrolled hyperinflammation and predisposition to cytokine storm that may develop [3,4].

It is thought that in COVID-19 infection, the virus attaches to the cells containing its receptor and enters the cell, causing damage [5]. Receptors are found in many systems, organs, and cells. These receptors have also been shown in pancreatic islet cells [6]. It is thought that severe infection may cause pancreatic damage, resulting in a decrease in pancreatic reserve and impaired regulation in diabetic patients.

Our study aimed to examine the effects of severe COVID-19 infection on metabolic parameters and blood sugar regulation in diabetic patients in the medium and long term.

2. Materials and Methods

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Study Design

The study is a retrospective cohort study conducted to investigate the effect of COVID-19 infection on patients with type 2 diabetes. Two groups of patients selected from patients who were admitted to internal medicine or endocrinology and metabolism outpatient clinics between 01/02/2021 - 01/05/2021, were hospitalized due to COVID-19 infection between 01/04/2020 - 01/07/2020 (Group 1) and did not have COVID-19 infection during this period (Group 2) were included in the study. The changes in control diabetes and other metabolic parameters of the patients after six months were compared as inter- and intra-group, and the differences between the groups were examined.

Ethical approval and Declaration

Approval was obtained from Kütahya University of Health Sciences, Faculty of Medicine, Non-Interventional Research Ethics Committee on 09.02.2022 with decision number 2022/02-13 before the study. The study was conducted in accordance with the latest version of the "Declaration of Helsinki" and the "Good Clinical Practice Directive".

Study Population

A total of 127 patients, including 79 women and 48 men, were included in the study; 64 of these patients had Covid-19 and 63 had no infection.

Inclusion criteria were defined as being a patient over 18 years of age and diagnosed with type 2 diabetes mellitus. Patients who were younger than 18 years of age, had active malignancy, developed diabetes after pancreatic surgery, had chronic liver disease, and chronic alcohol use were excluded from the study.

The patient group included diabetic patients who had COVID-19 during the first three months of the pandemic and then came to routine outpatient clinic control for diabetes. The control group included patients with type 2 diabetes over the age of 18 who did not have COVID-19 infection and were admitted to the outpatient clinic for diabetes control.

Laboratory Parameters

HbA1c, fasting plasma glucose (FPG), lipid profile (LDL, HDL, triglyceride, total cholesterol), ALT, creatinine, uric acid, TSH, amylase, and lipase were recorded retrospectively. The results of the patient's samples were analyzed at the Central Laboratory of Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital.

Age, gender, smoking history, height, body weight, duration of diabetes mellitus, medications, and comorbidities were recorded by analyzing the patient files.

HbA1C levels were measured immediately after blood samples were taken without waiting. Measurements were performed by high-pressure liquid chromatography (HPLC) with a Tosoh G8 HPLC Analyser (TosohBioscience, Inc., San Francisco, CA). Fasting blood glucose and lipid parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides) were measured on the day blood samples were taken without waiting. APG and lipid panels were measured with the original kits using a BeckmanCoulter AU680 instrument (BeckmanCoulter, Miami, FL, USA). The reference ranges of biochemical parameters were as follows: FPG 74-106 mg/dL, total cholesterol <200 mg/dl, HDL-cholesterol>40 mg/dL, LDL-cholesterol <100 mg/dl, and triglyceride<150 mg/dl.

Statistical Analysis

SPSS (Statistical Package for SocialScience) version 22 program was used to analyze the study data. The suitability of continuous variables to normal distribution was examined with Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed data were expressed as mean±standard deviation, non-normally distributed data were expressed as median and interquartile range (25-75 percent), and categorical variables were expressed as percentages. Differences between independent groups were compared using the Student t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical parameters were analyzed using the Chi-square test. In the correlation analysis, the Pearson correlation test was used for variables with normal distribution, and Spearman's correlation test was used for variables that did not show normal distribution. For all tests, a p-value of < 0.05 was considered statistically significant.

3. Results

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Considering the demographic characteristics of all patients, it is seen that there are a total of 127 participants, 79 women and 48 men. 62% of the participants are women and 37.8% are men. There is no statistically significant difference between patient groups and gender ($p>0.05$). The mean age of patients who had Covid 19 was 58.09 years and the standard deviation was 9.736. The average age of patients who did not have Covid 19 was 54.33 and the standard deviation was 10.799. There is a statistically significant correlation between patient groups and age ($p<0.05$). No statistically significant difference was detected between BMI and duration of diabetes in the patient groups ($p>0.05$) (Table 1).

Table 1. General characteristics of patient groups.

		All patients	Group 1		Group 2		
			Average	St deviation	Average	St deviation	p-value
Number of patients		127	64	-	63	-	0.945
Gender	Male	48	24	-	24	-	-
	Female	79	40	-	39	-	-
Age		56.23	58.09	9.736	54.33	10.799	**<0.05**
BMI		30,38	30.835	5.602	29.933	6.117	0.191
Duration of Diabetes diagnosis		9.06	8.847	6.939	9.278	7.686	0.952

No significant difference was detected between the patient groups in terms of comorbidities and medications used ($p>0.05$) (Table 2).

Table 2. Comorbidities and Medications Used in Patient Groups.

	Group 1		Group 2		p-value
	Yes	No	Yes	No	
Hypertension	36	28	32	31	0.538
Hyperlipidemia	23	41	26	37	0.537
Chronic Heart Disease	14	50	13	50	0.864
COPD	6	58	6	57	0.977
Baseline insulin	12	52	18	45	0.193
Bolus insulin	7	57	12	51	0.2
Metformin	39	25	45	18	0.212
Dpp4 inh	20	44	20	43	0.952
Sglt2 inh	14	50	23	40	0.07
Glitazone	6	58	2	61	0.273
Statin	13	51	20	43	0.142

When the common data of all patients was examined, no statistically significant difference was detected in FPG and triglyceride values at baseline and control ($p>0.05$). A significant difference was detected in HbA1c, total cholesterol, LDL cholesterol, and HDL cholesterol values ($p<0.05$). While the HbA1c value was found to be lower in the control, cholesterol values (total cholesterol, LDL cholesterol, HDL cholesterol) were found to be higher (Table 3).

Table 3. Change in diabetes control and cholesterol panel in all patients during 6 months.

	First control			Control after 6 months			
	Average	**Median**	**SD**	**Average**	**Median**	**SD**	**p-value**
APG	154.25	142.00	57.542	155.80	136.50	68.470	0.392
HbA1c	7.999	7.300	2.2409	7.681	7.000	2.0065	**0.001**
T. Cholesterol	196.18	194.00	59.846	208.20	208.00	48.267	**0.001**
LDL	115.330	114.000	47.7249	121.29	122.00	37.947	**0.019**
HDL	45.86	44.00	14.652	52.07	50.00	12.486	**.000**

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Triglycerides	190.70	159.00	137.463	191.80	156.00	109.602	0.572

The intragroups evaluation is given in Table 4. In group 1, HbA1c value was found to be statistically significantly lower, and cholesterol values (total cholesterol, LDL cholesterol, HDL cholesterol) were found to be higher ($p<0.05$). It was observed that HbA1c decreased from 8 to 7.7, total cholesterol increased from 193.11 to 216.13, LDL cholesterol increased from 113.7 to 124.9, and HDL cholesterol increased from 42.9 to 52.3. In Group 2, a significant difference was detected only in HbA1c and HDL cholesterol values ($p<0.05$). It was observed that HbA1c decreased from 7.9 to 6.9 and HDL cholesterol increased from 48.5 to 51.8. No significant difference was detected in other values (FPG, Total cholesterol, LDL cholesterol, Triglyceride) ($p>0.05$).

Table 4. 1. Change in diabetes control and cholesterol panel in group 1 during 6 months.

	Group 1						
	First control			Control after 6 months			
	Average	**Median**	**st deviation**	**Average**	**Median**	**st deviation**	**p-value**
APG	158.7	142.00	65.047	158.66	134.50	67.557	0.952
HbA1c	8.044	7.600	1.796	7.74	7.100	1.855	**0.003**
T.cholesterol	193.11	183.00	69.328	216.13	212.50	46.472	**.000**
LDL	113.7	111.500	53.534	124.93	124.00	34.296	**0.003**
HDL	42.96	40.50	15.944	52.3	51.50	11.625	**.000**
Triglycerides	199.5	157.00	170.697	196.44	175.50	99.812	0.355

Table 4. 2. Change in diabetes control and cholesterol panel in group 2 during 6 months.

	Group 2						
	First control			Control after 6 months			
	Average	**Median**	**st deviation**	**Average**	**Median**	**st deviation**	**p-value**
APG	149.66	142.00	48.712	152.85	139.00	69.827	0.12
HbA1c	7.961	7.100	69.827	7.621	6.900	2.572	**0.043**
T.cholesterol	199.1	202.00	49.618	200.16	201.00	49.087	0.492
LDL	116.878	117.00	41.881	117.71	122.00	41.191	0.804
HDL	48.52	48.00	12.921	51.84	49.00	13.409	**0.001**
Triglycerides	182.02	159.00	96.621	187.02	151.00	119.503	0.76

Insulin, c-peptide, and urine albumin levels were measured in all patients at follow-up to evaluate pancreatic reserve and the presence of nephropathy. No significant difference was detected in insulin, c-peptide, and spot urine albumin values between the groups ($p>0.05$) (Table 5).

Table 5. Comparison of Insulin, C peptide, and Albumin in Spot Urine.

	Group 1		Group 2		
	Average	**st deviation**	**Average**	**st deviation**	**p-value**
Insulin	11.5035	9.80208	12.8505	10.18689	0.27
C peptide	2.5706	1.06435	2.8596	1.57621	0.311
Albumin in spot urine	67.1204	158.5226	46.5533	149.0702	0.224

4. Discussion

In this study, we retrospectively analyzed the effects of the pandemic period and the disease on metabolic parameters in diabetic patients with COVID-19 infection. Our findings show that diabetic patients with COVID-19 infection do not have a significant deterioration in blood glucose regulation

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in the long term, but there is a significant increase in the cholesterol panel (total cholesterol and LDL cholesterol).

Diabetes has become an increasing health problem today. Individuals with diabetes are more vulnerable to infectious diseases, and these diseases generally have a more severe course. COVID-19 infection also confirms this situation. Type 2 DM patients have a high risk of developing severe COVID-19, and it is also known that the incidence of severe acute metabolic complications of diabetes, such as the development of new-onset diabetes, dysregulation, or diabetic ketoacidosis due to COVID-19, is increased [7-9]. Additionally, COVID-19 tends to be more severe in individuals with diabetes [10]. A study reported that 30-40% of patients hospitalized due to COVID-19, who required intensive care, and experienced mortality, had a diagnosis of diabetes [11]. However, information about the effect of diabetes control in the medium and long term after COVID-19 infection is not clear. It is known that the SARS-CoV-2 virus enters cells via the ACE-2 receptor, causing cellular damage. This mechanism can also damage pancreatic islet cells, potentially leading to pancreatitis [12]. In a study by Chen J et al, it was reported that no significant change was found in HbA1c values of diabetic patients after COVID-19 infection [13]. In our study, it was determined that there was no deterioration in diabetes regulation in the medium term in patients who had moderate or severe COVID-19 and received inpatient treatment in the hospital, on the contrary, there was an improvement. The reason for this was thought to be that blood glucose regulation was provided with close follow-up and treatment during hospitalization, and blood glucose levels approached the target values with short interval controls in the post-infection period.

The impact of restrictions implemented during the pandemic on diabetes control is another topic of debate. In the presence of restrictions, physical exercise becomes difficult, and a sedentary lifestyle is inevitable. It is known that a sedentary lifestyle has a negative impact on diabetes regulation [14]. In a study conducted in Northern India, no significant change in HbA1c was found in the period when restrictions were applied compared to the pre-quarantine period [15]. In contrast to this study, there are also studies showing a significant increase in HbA1c during the restriction period [16,17]. In our study, the mean HbA1c decreased from 7.9 to 6.9 in the patient group who did not have Covid-19.

The effects of COVID-19 infection on lipid metabolism are widely discussed in the literature. In a retrospective study by Qin et al., a decrease in total cholesterol and LDL cholesterol levels was found in COVID-19 patients [18]. In a review, it was stated that the change observed in most studies on the lipid profiles of COVID-19 patients was a decrease in cholesterol and apolipoprotein levels and an increase in triglycerides [19]. However, in our study, a significant increase in LDL cholesterol, total cholesterol, and HDL cholesterol levels was detected in diabetic patients with COVID-19. It is known that the development of atherosclerotic complications is highly likely in diabetic patients [20]. It is also known that dyslipidemia poses a high risk for the development of atherosclerosis and cardiovascular diseases [21]. It should be considered that the negative effect of COVID-19 infection on the lipid profile in the medium and long term will be a problem in terms of cardiovascular diseases and mortality.

Diabetes management during the pandemic period was ensured by patients continuing their regular check-ups and complying with diet and exercise recommendations. In this period, the decrease in patients' HbA1c levels can be evaluated as a result of regular follow-up and appropriate treatment management. However, further prospective studies are needed to assess the long-term effects of COVID-19 infection in diabetic patients. Yet, it is clear that the effect on lipid profile should be evaluated with larger and prospective studies.

Our study has some limitations. The average age of patients who had Covid-19 was higher than that of patients who did not have Covid-19. Healthier results could be obtained in a population with more balanced average ages. Additionally, the lack of objective data on patients' exercise habits created limitations in interpreting the results. Other limitations of our study are that it is a retrospective study and only 6-month data were evaluated. Longer-term and prospective studies will more clearly reveal the long-term effects of Covid-19 on diabetes.

5. Conclusions

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The Covid-19 pandemic poses a significant health threat to patients with diabetes. Infection prophylaxis, healthy lifestyle, and regular medical follow-up are critical in protecting diabetic patients from COVID-19 and its possible complications. In our study, it was determined that COVID-19 infection did not seriously disrupt metabolic processes in diabetic patients but caused an increase in cholesterol levels. Patients with diabetes should be followed closely in the post-infection period and complications should be minimized with appropriate treatment management.

Author Contributions: Each author contributed to the conception and design of the study, collection and analysis or interpretation of data, and writing.

Funding: This research received no external funding.

Institutional Review Board Statement: Approval was obtained from Kütahya University of Health Sciences, Faculty of Medicine, Non-Interventional Research Ethics Committee on 09.02.2022 with decision number 2022/02-13 before the study. The study was conducted in accordance with the latest version of the "Declaration of Helsinki" and the "Good Clinical Practice Directive".

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: !!!

Conflicts of Interest: The authors declare no conflicts of interest.

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