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# The Association between Pandemic Isolation and Glycemic Control and Biochemistry Parameters in Patients with Type 2 Diabetes

## ABSTRACT

**Objective: COVID-19 lockdown caused many people with chronic diseases to delay their follow-up and worsen their metabolic parameters. This study aimed to investigate the effect of the COVID-19 pandemic period on the glycemic control and biochemistry parameters of patients with type 2 diabetes mellitus (T2DM).**

**Materials and methods: The data of 347 T2DM patients covering the period before and after the lockdown (March–June 2020) was retrospectively analyzed. HbA1c and fasting plasma glucose (FPG), renal function tests and microalbuminuria measurements were compared. All statistical analyses and power analysis were performed with IBM SPSS Statistics version 23.0.**

**Results: Of 347 patients, 216 (62.2%) were female and the mean age was 58.82 ± 10.47 years. One hundred eighty five (53.3%) of the individuals have been using insulin and oral antidiabetic together and those treated with insulin alone were excluded at the data collection phase of the study. HbA1c, FPG, urea, creatinine, microalbumin in spot urine and alb/crea in spot urine increased in the pandemic period compared to pre-pandemic period, creatinine measurement decreased in spot urine ($p < 0.05$) except the ketone in urine between the two periods. HbA1c ($r = 0.728$, $p < 0.01$), creatinine ($r = 0.8458$, $p < 0.01$), microalbumin in spot urine ($r = 0.773$, $p < 0.01$) and spot urine alb/crea ($r = 0.796$, $p < 0.01$) measurements were highly, positive and statistically significant.**

**Conclusions: As in all chronic diseases, T2DM patients should be followed up regularly in order to prevent morbidities in extraordinary situations such as pandemics. (Clin Diabetol 2022; 11; 6: 401–408)**

**Keywords: type 2 diabetes, COVID-19 lockdown, HbA1c, renal functions**

## Introduction

Diabetes mellitus (DM) is a health problem that is increasing in importance due to its prevalence and the burden caused. Currently, it seems to be a global epidemic. The coexistence of two global pandemics — COVID-19 and diabetes mellitus — has significant clinical implications and negative impacts on morbidity and mortality [1]. According to many large-scale studies and the American Diabetes Association, HbA1c level should be 7% and below in order to prevent the complications [2]. If DM isn't well controlled, it can lead to serious complications such as coronary artery disease, peripheral artery disease, cerebrovascular diseases, nephropathy, retinopathy and neuropathy in the long term and complications of diabetes cause overuse of health centers, increased health costs and

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loss of workforce [3, 4]. The COVID-19 which emerged as a respiratory disease caused by a new coronavirus and defined by the World Health Organization (WHO) as a pandemic due to spreading of infection rapidly and profoundly on March 11, 2020. From the first case to June 2022, there were approximately 6.3 million deaths, most of them elderly and having chronic disease. In order to prevent the high demand for health services shortly after the detection of the first case in our country, people aged 65 and over and those with T2DM, hypertension, chronic pulmonary disease, cardiovascular disease, renal and hepatic failure and immunocompromised patients were banned to go out by the governments [5]. Clinical follow-up and glycemic control were disrupted in patients with T2DM due to these restrictions and lockdown. A meta-analysis provides evidence that severe COVID-19 is associated with increased blood glucose, and HbA1c was slightly higher in patients with severe COVID-19 than those with mild ones [6]. In another study in patients with T1DM, mean HbA1c in the lockdown period (10 ± 1.5%) was statistically higher that that from pre-lockdown period HbA1c (8.8 ± 1.3%) [7]. On the other hand, in an Indian study, significant change was not noted in HbA1c and body weight before and after lockdown in a study with T2DM patients, despite the decrease in using drugs, physical activity, irregular eating habits [8]. According to our clinical observations, patients with T2DM, most of whom are elderly and followed as outpatients and commonly on oral antidiabetics, were mostly influenced by social restrictions. There are few studies about the impact of the pandemic on HbA1c levels of patients with T2DM as well as on renal function tests. From this viewpoint, we conducted a research to investigate whether the COVID-19 pandemic process has significant effects on the glycemic control, blood and urine laboratory measurements of patients with T2DM as a result of the restrictions imposed.

## Material and methods

### Study design and subjects

This single-center, retrospective analytical study was conducted with the same outpatients who applied to Family Medicine outpatient clinics of the Diskapi Yildirim Beyazit Health Application and Research Center, Health Sciences University, Ankara for visit in the period before and after the lockdown (March–June 2020). The data of the patients who applied between March 1, 2019 and March 1, 2020 (pre-pandemic period) and between June 1, 2020 and June 1, 2021 (pandemic period) were analyzed. The examined patients could not regularly attend outpatient visits due to fear of contamination or various restrictions as during the pandemic. Patients with T2DM diagnosis, over 18 years of age, HbA1c, fasting plasma glucose (FPG), blood urea nitrogene (urea), creatinine, urinalysis and microalbuminuria in spot urine were included in the study by taking their sociodemographic information from the hospital data system. Patients under the age of 18, diagnosed with T1DM, whose T2DM treatment has been changed during the pandemic, who had COVID-19 infection, and patients with missing data in processing system of the hospital were not included in the study. Patients' HbA1c and fasting plasma glucose at these two time intervals, as well as renal function tests and microalbuminuria measurements were compared. All patients who applied within the specified period and whose blood and urine tests were full data available were included in the study. Patients using only insulin were not followed up by family medicine doctors, so they were excluded from the study.

### Outcome measures

The primary endpoint of this study was the mean difference in HbA1c before and after lockdown period. The secondary endpoints included mean change in FPG, urea, creatinine, urinalysis and microalbuminuria in spot urine. The model of antidiabetic treatment used by the patients was categorized as 1) oral antidiabetics (OAD) group, and 2) OAD plus insulin group. Patients using only insulin were not followed up by family medicine, so they were excluded from the study.

### Statistical analysis

SPSS 23.0 program was used for the analysis of the study data. Parametric test techniques were used to perform the analysis. Related samples t-test was used to determine the difference between pre-pandemic and pandemic blood and urine measurements of the patients, and McNemar test was used for categorical variable of ketone in urine. A two-factor ANOVA test was used to determine the joint effect of the pandemic process and gender, age, and insulin use status on the differentiation between pre-pandemic and pandemic blood and urine measurements of the patients. Significance levels were accepted as 0.01 and 0.05.

### Ethical considerations

The research does not conflict with the principles stated by the Declaration of Helsinki of 1975, as revised in 2013, and the principles of Good Clinical Practice. The study was reviewed and approved by the Clinical Research Ethics Committee of Diskapi Yildirim Beyazit Health Application and Research Center, Health Sciences University, Ankara in September 20, 2021 with the

**Table 1. Demographic Data of the Patients Included in the Study (n = 347)**

| Feature | Variables | n | % |
|---|---|---|---|
| Gender | Female | 216 | 62.2 |
| | Male | 131 | 37.8 |
| Age | 18–44 | 34 | 9.8 |
| | 45–59 | 155 | 44.7 |
| | 60–74 | 136 | 39.2 |
| | 75–89 | 22 | 6.3 |
| Form of treatment | OAD + insulin | 185 | 53.3 |
| | OAD | 162 | 46.7 |

OAD — oral antidiabetic drug

104/14 decision number. An informed consent was obtained from all human adult participants. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Results

### Participants' characteristics

Three hundred forty seven patients with T2DM aged 18–89 (mean age 58.82 ± 10.47 years) were included, of which 216 (62.2%) were female and 131 (37.8%) were male. Of the patients, 34 (9.8%) were between the ages of 18–44, 155 (44.7%) were between the ages of 45–59, 136 (39.2%) were between the ages of 60–74, and 22 (6.3%) were between the ages of 75–89. While 162 (46.7%) of the patients were using only oral antidiabetic, 185 (53.3%) were using both oral antidiabetic and insulin therapy (Tab. 1).

### Glycemic control

The average HbA1c level of 347 patients was 7.85 (± 1.47) pre-pandemic period and 8.42 (± 1.77) in pandemic period. The difference between the two groups was statistically significant in favor of worsening the parameters during pandemic period. The difference between pre-pandemic and pandemic HbA1c ($p < 0.000$), FPG ($p < 0.000$), urea ($p < 0.000$), creatinine ($p < 0.005$), microalbumin in spot urine ($p = 0.038$), creatinine in spot urine ($p = 0.025$), albumin in spot urine and alb/crea ($p < 0.000$) parameters was statistically significant (Student *t*-test, ANOVA). HbA1c, FPG, urea, creatinine, microalbumin in spot urine and alb/crea in spot urine increased in pandemic period compared to pre-pandemic period, whereas creatinine levels in spot urine decreased. There was no significant change in the ketone level in the urine between the two periods ($p > 0.05$) (McNemar test) (Tab. 2).

When Pearsons' correlation test was applied to evaluate the relation between laboratory parameters of pre-pandemic and pandemic period, HbA1c ($r = 0.728$, $p < 0.01$), creatinine ($r = 0.8458$, $p < 0.01$), microalbumin in spot urine ($r = 0.773$, $p < 0.01$) and spot urine alb/crea ($r = 0.796$, $p < 0.01$) measurements were highly, positive and statistically significant. In addition, there was a moderate correlation between pre-pandemic and pandemic period FPG ($r = 0.544$, $p < 0.01$), urea ($r = 0.664$, $p < 0.01$) and spot urine creatinine ($r = 0.446$, $p < 0.01$). There was a positive and linear relationship (Fig. 1).

The pre-pandemic and pandemic period blood and urine measurements of the patients participating in the study were compared individually with age and gender; however, no statistically significant difference was found ($p > 0.05$).

In terms of alb/creatinine measurement in spot urine, a higher increase was observed in male patients during the pandemic period compared to the pre-pandemic period ($p = 0.011$). However, there was no

**Table 2. Comparison of Blood and Urine Values Before and After the Pandemic (n = 347)**

| Laboratory parameters | Mean ± SD | | P-value | r |
|---|---|---|---|---|
| | Pre-pandemic | Post-pandemic | | |
| HbA1c | 7.85 ± 1.47 | 8.42 ± 1.777 | 0.000* | 0.728 |
| FPG | 158.59 ± 52.487 | 177.48 ± 69.107 | 0.000* | 0.544 |
| Urea | 31.33 ± 9.862 | 33.16 ± 10.356 | 0.000* | 0.664 |
| Creatinine | 0.75 ± 0.221 | 0.77 ± 0.221 | 0.005* | 0.845 |
| Microalbumin in spot urine | 5.24 ± 11.22 | 6.38 ± 12.4 | 0.038** | 0.083 |
| Creatinine in spot urine | 118.55 ± 62.278 | 111.82 ± 62.916 | 0.025** | 0.773 |
| Spot alb/crea in urine | 48.39 ± 101.57 | 64.55 ± 129.34 | 0.000* | 0.446 |
| Ketone in urine *** | 0.0432 ± 0.20366 | 0.049 ± 0.21616 | 0.85 | 0.796 |

*Student t test; *$p < 0.01$; ** $p < 0.05$ was considered statistically significant; ***McNemar test was used for ketone in urine
FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; SD — standard deviation

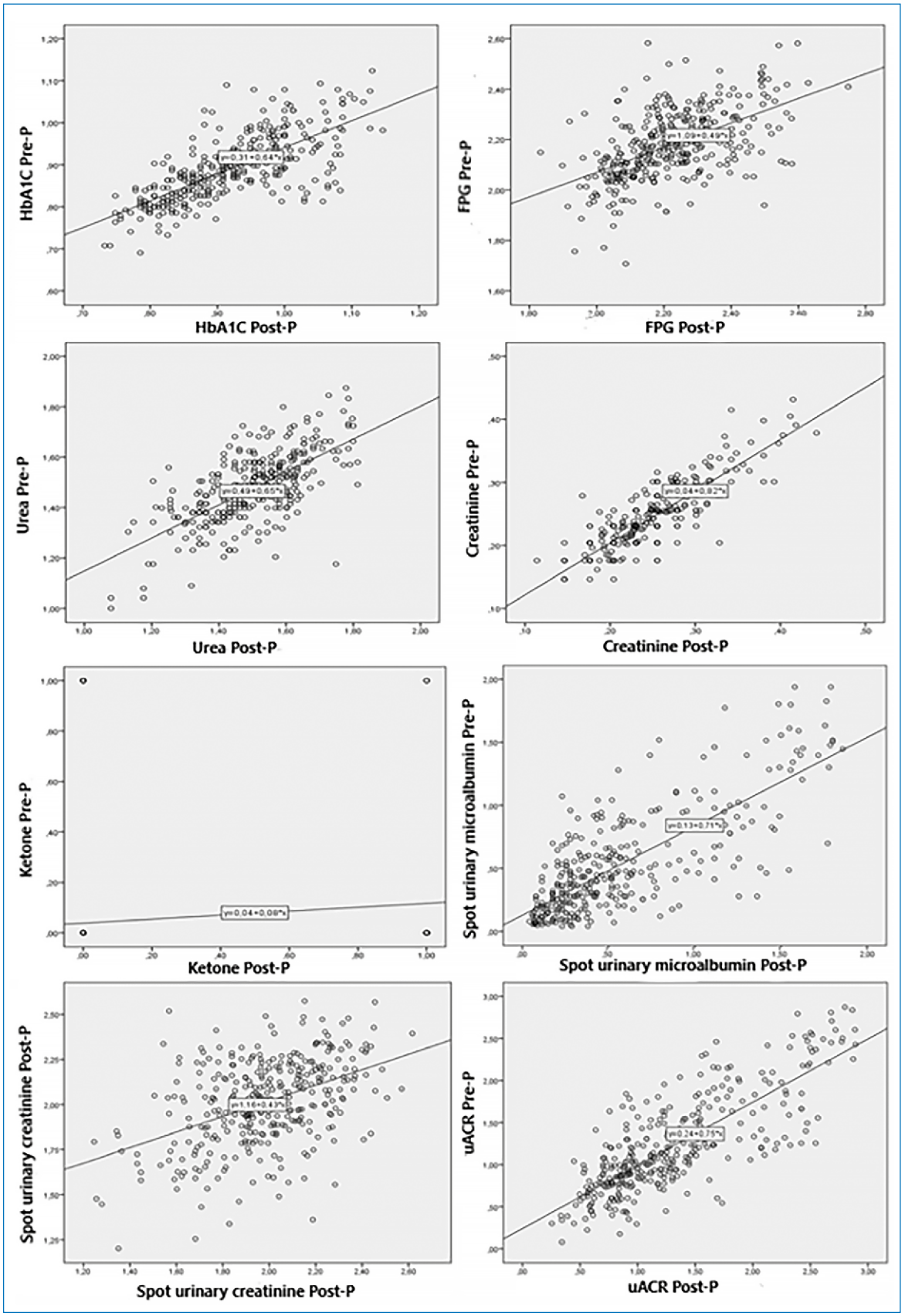


**Figure 1.** The Correlation Graphs of Blood and Urine Measurements of Pre-pandemic (Pre-P) and Pandemic Period (Post-P)
A positive linear correlation was found in all urine and blood measurements (except for ketone in urine).
FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; uACR — urine albumin creatinine ratio

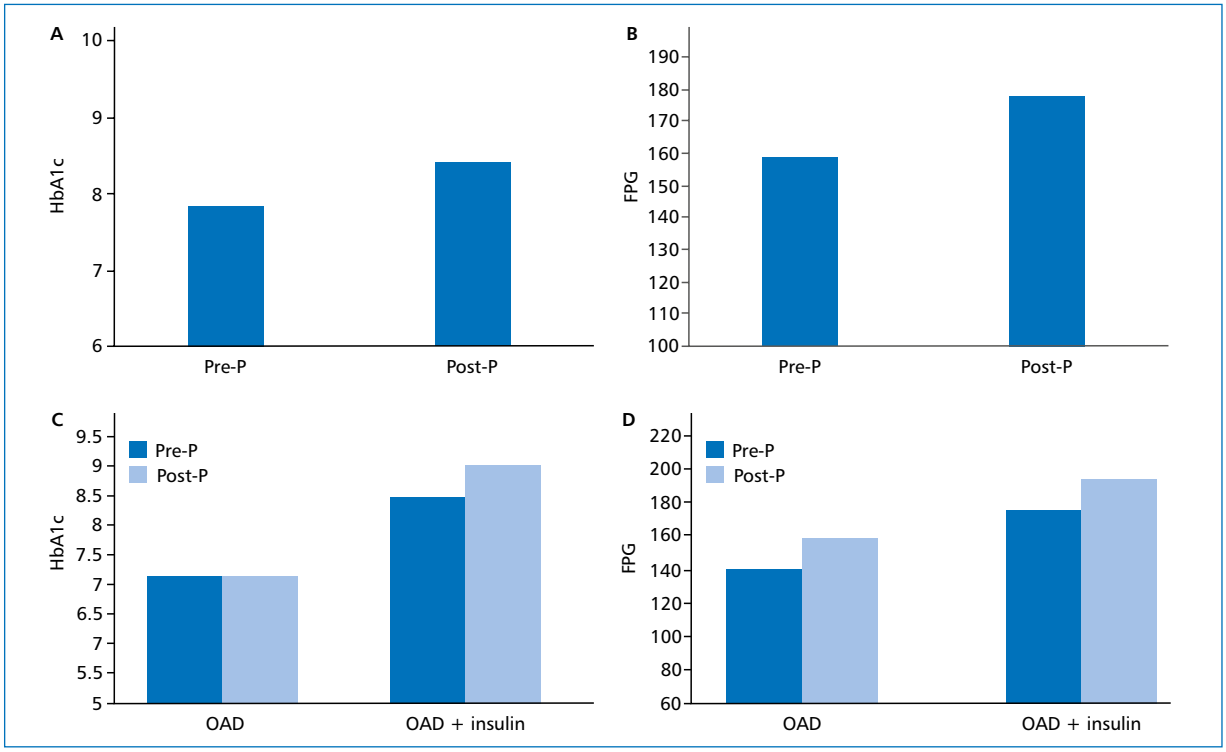


**Figure 2.** Comparison of HbA1c and FPG of Patients in Pre-pandemic and Pandemic Period
**A.** Pre-pandemic (Pre-P) and pandemic (Post-P) HbA1c ($p = 0.00$) measurements of T2DM patients. **B.** FPG measurements ($p = 0.00$) of T2DM patients. **C.** Pre-P and Post-P HbA1c of patients using only OAD and both OAD and insulin ($p = 0.469$) **D.** Pre-P and Post-P FPG of two patient groups ($p = 0.60$)
FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; OAD — oral antidiabetic T2DM — type 2 diabetes mellitus

significant difference in terms of gender in other laboratory parameters. There was no significant difference in pre- and post-pandemic blood and urine parameters in terms of treatment modalities (only OAD or a combination of OAD and insulin), also ($p > 0.05$). (Fig. 2)

## Discussion

We have experienced many extraordinary situations such as prohibitions, restrictions, obligations (mask, vaccine, etc.) and even lockdown with the warnings of the WHO and the order of the government, during the pandemic [9]. People with chronic diseases, elderly and people with impaired immunity could not regularly attend outpatient clinics due to fear of contamination or various restrictions. This retrospective, single-center study evaluated the effect of these lockdown periods on glycemic control and renal function in a population of patients with T2DM. The family medicine outpatient clinics acted as a center that people with chronic diseases or suitable for outpatient examination were able to apply easily during the pandemic. Therefore, they were general reference points for control of patients with T2DM, excluding patients using insulin 2–4 times a day. Accordingly, our sample may reflect the vast majority of patients.

In this study, not only a significant increase in HbA1c and FPG levels was observed but also glycemic index of patients who was negatively affected by the restrictions in the pandemic. There is limited availability of studies presenting an increase in HbA1c levels during the pandemic in patients with T2DM. In the study of Önmez et al. [9] in Turkey, an increase in HbA1c and FPG of patients with T2DM was found, but it was not statistically significant as in the study of Ruissen et al. [10]. These results are attributed to the fact that screening of the 8–11-week isolation period and the measured HbA1c might not reflect the glycemic change accurately [9]. Lockdown in India did not cause a major change in the overall glycemic control in another cross-sectional study and it was attributed to a general increase in healthy eating habits [8]. In the study of Fernández et al. [11] with T1DM patients , a decrease in both HbA1c and mean FPG was found, and the authors attributed those results to the consumption of healthy products and the longer time devoted to treatment. Even the patients having a healthy diet at home and the opportunity to do more exercise instead of eating ready-made office meals resulted in a significant decrease in HbA1c [11]. Fisher et al. [12] suggested the increased stress and pressures associated with the

pandemic as the cause of worsening glycemic control in the study populations. The common cause of worsening may be due to the malnutrition and decrease in physical activity, weight gain and worsening of other metabolic parameters [7, 13]. Lockdown determined a short-term worsening in glycemic index in these populations according to a systematic review [14]. In our study, a significant increase was found in HbA1c and FPG, and glycemic control was shown to be adversely affected for a relatively long follow-up period, because we had observed one-year before and one-year after the lockdown period. This situation made us think that although the full-restriction period in the pandemic in our country was short-lived, its effects on the course of chronic diseases such as T2DM lasted for a long time. Maintaining good glycemic control is important for these patients. Given that people with T2DM are also candidates for new cases of COVID-19, it is likely that these people will also face serious complications and 2.16-fold increased mortality when hospitalized [15].

Failure to follow-up T2DM had caused not only poor glycemic index, but also renal complications such as microalbuminuria. It was observed that significant increase in HbA1c levels recorded in our study were accompanied by deterioration in renal function tests. In the study of Önmez et al. [9], however, no significant change was observed in urea and creatinine, Yeter et al. [16] found a significant increase in urea and creatinine rates in chronic renal failure patients treated with peritoneal dialysis. In a study by Hakroush et al. [17] a decrease was found in urea and creatinine, but the mean proteinuria measurement was found to be insignificant in patients who required renal biopsy. In our study, it was shown that urea, creatinine, microalbumin in spot urine, creatinine and albumin/creatinine levels were negatively affected by the lockdown. It is a known fact that the risk of diabetic nephropathy is higher in patients with poor glycemic control [18]. According to the literature, it was seen that many studies didn't focus on how renal functions are affected by isolation. Our study also showed the negative effects of poor glycemic control on the kidneys. Of course, we know that poor glycemic control is not the only reason for the deterioration of microalbuminuria and urea-creatinine ratiowithout the development of diabetic nephropathy. Attribution of worsening of renal function only to diabetes may be a bias. There are direct-action factors such as less fluid intake, poor diet style, and multiple drug use that affect renal functions. However, it would not be wrong to say that poor glycemic control may be the most important factor that worsens renal dysfunction in cases where all diabetes-related indicators of patients deteriorate.

In studies conducted with patients diagnosed with T1DM, in terms of diabetic ketoacidosis (DKA), it was observed that admissions to the hospital with DKA increased during the isolation period [19–21]. In the study of Chao et al. [22], with T2DM patients, it was observed that there was an increase in hospital admissions with DKA during the pandemic in young patients with T2DM. In our study, ketone in spot urine was screened for DKA, but no statistically significant result could be obtained. Measuring of the ketone only in the urine did not provide much information in terms of DKA. This is one of the limitations of our study. Karatas et al. [23] compared patients with T2DM according to gender and could not find a statistically significant difference. Capaldo et al. [24] described that glycemic variability decreased significantly in patients with T1DM, and the change was associated with $< 35$ years of age, male gender, and multiple daily insulin injection (MDI) therapy. In another study, it was shown that there are statistically significant differences between genders in terms of nutrition and diet compliance in patients with T2DM [25]. In our study, no statistically significant result was found when the pandemic period and gender were evaluated together. Fisher et al.'s [12] study found that the effect of age was stronger in adults with T2DM than in adults with T1DM. It was observed that the pandemic caused more difficulty in managing their diabetes and more frequent hyperglycemia only for adults with T2DM, and there was no significant relationship between these variables in patients with T1DM. A study has shown that the groups most affected by the pandemic are patients over 60 years of age, who have risk factors such as hypertension, diabetes, or the presence of cardiovascular disease [26]. In the subgroup analysis by Park et al. [27], it was observed that the mean HbA1c level increased significantly in participants younger than 50 years of age. In the study of Biamonte et al. [13] with patients with a mean age of 70 years, glycemic control showed a poor course. In our study, statistically significant results could not be obtained when age and pandemic period were evaluated together. This may be due to the fact that the 1-year period was scanned in the study, the duration of diabetes complications was long, and the duration of diabetes diagnosis of the patients was unknown. More and more detailed studies should be conducted to investigate the effect of the pandemic period on glycemic control in patients with diabetes. Ten percent of the patients participating in the study of Sankar et al. [8] did not use their drugs partially or completely; they were predominantly in younger age groups, most of these patients used only OAD, and glycemic control was adversely affected. Shah et al. [28], in their study evaluating hypoglycemia, reported that patients treated with insulin had lower FPG compared

to metformin and sulfonylurea combinations. When Biamonte et al. [8] compared the clinical features of the insulin- and non-insulin-treated groups, they found that T2DM duration, baseline HbA1c, heart failure and retinopathy were higher in the insulin-treated group. In our study, the variation in blood and urine parameters was examined in terms of the pandemic process and using insulin with OAD or OAD only, but no significant effect was found between the pandemic process and the use of insulin on the variation in blood and urine measurements. This may be due to the lack of detailed information about the OAD and insulin doses used by the patients in our study.

One of the limitations of our study is that our study does not include a detailed evaluation of the factors that may affect the glycemic control of the patients, such as lifestyle changes during isolation, dietary compliance, body mass index, treatment duration of diabetes, comorbidities, drugs used, additional diseases, blood pressure, access to drugs and detailed information about drugs and stress factor. Another limitation is conducting the study retrospectively.

## Conclusions

The restrictions applied in the COVID-19 pandemic have caused some problems in terms of health, especially in terms of chronic diseases. Our study showed that the restrictions and lockdown period negatively affects glycemic control regardless of age, gender, and the type of treatment in T2DM patients. The study pointed out that if global events such as pandemics occur, it is necessary to keep in mind being more careful in the control of patients with chronic diseases such as T2DM. In this respect, we hope that evidence provided by this study will be useful in healthcare practice.

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## Conflict of interest

None declared.

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