

Retrospective Study on the Impact of COVID-19 Lockdown on Patients with Type 2 Diabetes in Northern Taiwan

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Background: During the COVID-19 pandemic, the national lockdown had a significant impact on healthcare systems and diabetes management. The results of relevant studies were inconsistent. The aim of the study was to investigate the impact of lockdown on glycemic control among patients with type 2 diabetes mellitus (T2D) in Taiwan.

Methods: This was a retrospective study conducted in a single regional hospital in Northern Taiwan. The clinic characteristics of the patients were summarized. Anthropometric and biochemical data before and after the lockdown were collected and analyzed. Stepwise multiple regression analysis was performed to identify the independent determinants of variables, including baseline characteristics and laboratory parameters, for the changes in glycated hemoglobin (HbA1c).

Results: A total of 943 (females 48.5%) patients with T2D were enrolled. The mean age of the patients was 60.6±12.3 years, with a mean HbA1c of 7.0±1.0%, a mean diabetes duration of 7.3±4.6 years, and a mean body mass index (BMI) of 26.5±4.5 kg/m². The overall means of HbA1c and fasting blood glucose were significantly improved after the lockdown compared to before (7.0±1.0 vs 6.8±0.9, $p<0.001$ and 132.2±33.3 vs 124.4±30.0, $p<0.001$, respectively). The proportion of patients achieving HbA1c target ($\leq 7\%$) was higher after the lockdown compared to before (61.5% vs 68.9%, $p<0.001$). Stepwise multiple regression analysis revealed that baseline HbA1c before the lockdown was a positive contributor to the change in HbA1c after the lockdown, whereas BMI and co-morbidity with dyslipidemia were negative contributors (standardized coefficient +0.16, $p<0.001$; -0.07, $p=0.025$; -0.12, $p=0.001$, respectively).

Conclusion: Our study highlights the benefits of lockdown measures on diabetic control in Northern Taiwan as a single-center experience with the improvement of HbA1c and fasting blood glucose. Understanding these consequences of national lockdown can help healthcare providers to improve diabetes care during the pandemic.

Keywords: COVID-19 lockdown, type 2 diabetes mellitus, glycemic control

Introduction

Since December 2019, millions of people worldwide have been infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused a pandemic.^{1,2} Learning from its experience with the 2003 SARS epidemic, the Taiwan government established a public health response system for rapid and effective prevention actions in face of this new crisis.^{3,4} There were some sporadic cases and small-scale local outbreaks of the coronavirus disease 2019 (COVID-19) in 2019 and 2020. However, in May 2021, a large-scale community outbreak of COVID-19 erupted in Taiwan, prompting the Central Epidemic Command Center (CECC) of Taiwan to declare a state of emergency and implemented a national lockdown between May 19th and July 27th, 2021 (a total of 69 days), to halt the spread of the disease.⁵ The national lockdown in Taiwan included a set of strict measures that restricted the free movement of people (except those with authorization), required the closure of most public places, and shortened the opening hours of shops. Citizens were required to stay at home and were not permitted to dine in restaurants or exercise in parks and gyms.

Healthcare services were limited to emergency care only and with prescription refills for patients with chronic or essential diseases.

The lockdown imposed strict restrictions on people's movements, resulting in significant changes in lifestyle, mental health, and behaviors, including alterations in diet, exercise levels, and working activities. These changes may have a profound impact on the population's metabolic health, especially for individuals with type 2 diabetes mellitus (T2D), where diet and physical activity play a crucial role in disease management.⁶ However, the results of relevant studies investigating the impact of lockdown on diabetic control have been inconsistent and varied across different countries. While some studies have found worse glycemic control in patients with diabetes during or after lockdown, others have reported improving glycemic control or no significant difference.^{7–10}

During the COVID-19 pandemic, several studies had examined the impact of national lockdowns on metabolic control in patients with diabetes mellitus. Some studies had found a negative impact on glycemic control in patients with diabetes, which may be attributed to changes in diet, disruptions in daily routines, decreased physical activity, increased sedentary behavior, and stress levels during the lockdown period. On the other hand, other studies had reported improvements in metabolic control or no significant difference in glycated hemoglobin (HbA1c) levels.^{8,9,11} For instance, a 2022 meta-analysis of eleven studies from different countries examined the effects of COVID-19 lockdown on glycemic control and lipid profiles in patients with T2D. The analysis revealed a significant increase in HbA1c levels, fasting blood glucose (FBG), and body mass index (BMI) due to the lockdown, but the effect on lipid parameters was inconsistent.⁷ Another 2022 meta-analysis of 59 studies examined the impact of COVID-19 lockdown on glycemic control in people with both type 1 and 2 diabetes. The results showed small improvements across multiple outcomes of glycemic control, but no statistically significant difference in changes in HbA1c.¹⁰

After reviewing the literature, we found a lack of related studies investigating the impact of lockdown on glycemic control and metabolic profiles among patients with T2D in Taiwan. Therefore, the study aims to fill this gap by exploring the impact of lockdown on glycemic control and metabolic profiles in this population. The results of the study could provide valuable insights for public health authorities and healthcare providers on how to improve glycemic control among their patients.

Materials and Method

Study Designs and Patients

This retrospective study was conducted at a single regional hospital in Northern Taiwan and aimed to investigate the impact of the COVID-19 lockdown on glycemic control and metabolic profiles in patients with T2D. The study reviewed the medical records of 943 outpatients with T2D who received regular antidiabetic treatment and follow-up with laboratory tests every 2–3 months, specifically three months before (February 2021 to May 2021) and three months after the lockdown (August 2021 to October 2021), from the clinics of three endocrinologists. The data and information on the 943 T2D patients, including their relevant specifics, were provided in [Table 1](#). Patients with type 1 diabetes, prediabetes, or gestational diabetes were excluded from the study. Various patient characteristics such as age, gender, body weight, BMI, diabetes duration, blood pressure, smoking status, regular exercise habits, antidiabetic medications, microvascular complications, and comorbidities were investigated. Patients' declarations were used to obtain information on smoking status and regular exercise habits. Regular exercise habits were defined as practicing at least 30 minutes of moderate activity per day.¹²

We compared the results of laboratory tests before and after the lockdown, including HbA1c levels, FBG, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr), serum glutamate pyruvate transaminase (S-GPT), urine albumin-creatinine ratio (uACR), and the proportion of individuals achieving HbA1c target. Achieving $\text{HbA1c} \leq 7\%$ was considered the glycemic target.¹³ Renal function was evaluated as estimated glomerular filtration rate (eGFR) using the MDRD (modification of diet in renal disease) study equation.¹⁴ The study was approved by the Institutional Review Board of Taiwan Adventist Hospital, Taipei, Taiwan (approval number: 111-E-07) and conducted in accordance with the Declaration of Helsinki.

Table 1 Clinic Baseline Characteristics by Gender of 943 Patients with Type 2 Diabetes

Variable	Total	Female	Male	P value
Persons	n=943	n=457 (48.5%)	n=486 (51.5%)	–
Age	60.6 ± 12.3	61.9 ± 12.8	59.4 ± 11.7	0.001*
HbA1c (%) before lockdown	7.0 ± 1.0	7.0 ± 1.0	7.0 ± 1.0	0.900
Proportion of individuals achieving HbA1c target ≤7%	580 (61.5%)	284 (62.1%)	296 (60.9%)	0.696
Diabetes duration (years)	7.3 ± 4.6	7.4 ± 4.7	7.2 ± 4.5	0.596
Weight (kg)	71.2 ± 15.2	64.4 ± 12.5	77.5 ± 14.7	<0.001*
BMI (kg/m ²)	26.5 ± 4.5	25.9 ± 4.5	27.0 ± 4.4	<0.001*
Smoker (yes)	82 (8.7%)	14 (3.1%)	68 (14.0%)	<0.001*
Exercise (yes)	136 (14.4%)	41 (9.0%)	95 (20.0%)	<0.001*
Hypertension	522 (55.4%)	236 (51.6%)	286 (58.8%)	0.026*
Dyslipidemia	767 (81.3%)	377 (82.5%)	390 (80.2%)	0.377
Diabetic nephropathy	259 (27.5%)	116 (25.4%)	143 (29.4%)	0.165
Diabetic retinopathy	166 (17.6%)	78 (17.1%)	88 (18.1%)	0.676
Diabetic neuropathy	88 (9.3%)	37 (8.1%)	51 (10.5%)	0.206
Coronary arterial disease (yes)	97 (10.2%)	34 (7.4%)	63 (13.0%)	0.005*
Stroke (yes)	36 (3.8%)	22 (4.8%)	14 (2.9%)	0.122
Heart failure (yes)	33 (3.5%)	24 (5.3%)	9 (1.9%)	0.004*
Cancer (yes)	55 (5.8%)	41 (9.0%)	14 (2.9%)	<0.001*
Metformin	750 (79.5%)	351 (76.8%)	399 (82.1%)	0.044*
Pioglitazone	173 (18.3%)	97 (21.2%)	76 (15.6%)	0.027*
Sulphonylurea	520 (55.1%)	232 (50.8%)	288 (59.3%)	0.009*
SGLT2-i	271 (28.7%)	125 (27.4%)	146 (30.0%)	0.362
DPP4-i	461 (48.9%)	214 (46.8%)	247 (50.8%)	0.220
AG-i	38 (4.0%)	19 (4.2%)	19 (3.9%)	0.847
GLP-1 RA	30 (3.2%)	17 (3.7%)	13 (2.7%)	0.361
Insulin	88 (9.3%)	48 (10.5%)	40 (8.2%)	0.231

Note: Values are presented as mean ± standard deviation or number (%). *A p-value less than 0.05 was considered statistically significant.

Abbreviations: HbA1c, glycated hemoglobin; BMI, body mass index; SGLT2-i, sodium-glucose co-transporter 2 inhibitor; DPP4-i, dipeptidyl peptidase-4 inhibitor; AG-i, α-Glucosidase inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist.

Statistics Analysis

The data were collected and entered into the computer by a trained hospital staff member. Continuous variables were expressed as the mean ± standard deviation and analyzed using the two-sample *t*-test, while categorical variables were presented as numbers (percentage) and analyzed using the Chi-square test. Multiple regression analyses were performed to assess the degrees of association among independent variables, including baseline characteristics and laboratory parameters, for changes (before-after) in HbA1c. A p-value less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS statistical software (version 22.0, IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

A total of 943 patients with T2D were enrolled in the study, including 457 females (48.5%). The mean age of the patients was 60.6 ± 12.3 years, with a mean HbA1c of $7.0 \pm 1.0\%$, a mean diabetes duration of 7.3 ± 4.6 years, and a mean BMI of 26.5 ± 4.5 kg/m². Table 1 summarizes the clinic baseline characteristics of the group, including smoking status, regular exercise habits, antidiabetic medications, microvascular complications, and comorbidities. Compared to the male group, the female group had statistically significant differences in older age (61.9 ± 12.8 vs 59.4 ± 11.7 ; $p=0.001$), lower body weight (64.4 ± 12.5 vs 77.5 ± 14.7 ; $p<0.001$) and BMI (25.9 ± 4.5 vs 27.0 ± 4.4 ; $p<0.001$), less percentage of smokers (3.1% vs 14.0%; $p<0.001$) and regular exercisers (9.0% vs 20.0%; $p<0.001$) and lower prevalence of hypertension (51.6% vs 58.8%; $p=0.026$) and coronary arterial disease (7.4% vs 13.0%; $p=0.005$), but higher percentage of heart failure (5.3% vs 1.9%; $p=0.004$) and cancer (9.0% vs 2.9%; $p<0.001$).

Figure 1 depicts the proportion of antidiabetic medications used by females and males, showing that the use of metformin and sulphonylurea was significantly higher in the male group (76.8% vs 82.1%; $p=0.044$ and 50.8% vs 59.3%; $p=0.009$, respectively); On the other hand, the use of pioglitazone was significantly higher in the female group (21.2% vs 15.6%; $p=0.027$).

Outcomes

Table 2 presents the anthropometric and biochemical data before and after the lockdown. Compared to the period before the lockdown, the overall means of HbA1c levels and FBG were significantly improved after the lockdown (7.0 ± 1.0 vs 6.8 ± 0.9 , $p<0.001$ and 132.2 ± 33.3 vs 124.4 ± 30.0 , $p<0.001$, respectively). Moreover, the proportion of individuals achieving the HbA1c target ($\leq 7\%$) was higher after the lockdown (61.5% vs 68.9%, $p<0.001$). However, there was no statistically significant difference with regards to BMI, body weight, blood pressure, lipid profiles, kidney function, liver function, and uACR before and after the lockdown.

Figure 2 illustrates the mean HbA1c and the proportion of individuals achieving HbA1c target ($\leq 7\%$) for females and males before and after the lockdown. The mean HbA1c was significantly improved in both females and males after the lockdown compared to the period before the lockdown (7.0 ± 1.0 vs 6.8 ± 1.0 , $p=0.004$; 7.0 ± 1.0 vs 6.8 ± 0.9 , $p<0.001$, respectively). Similarly, the proportion of individuals achieving HbA1c target ($\leq 7\%$) was significantly higher after the

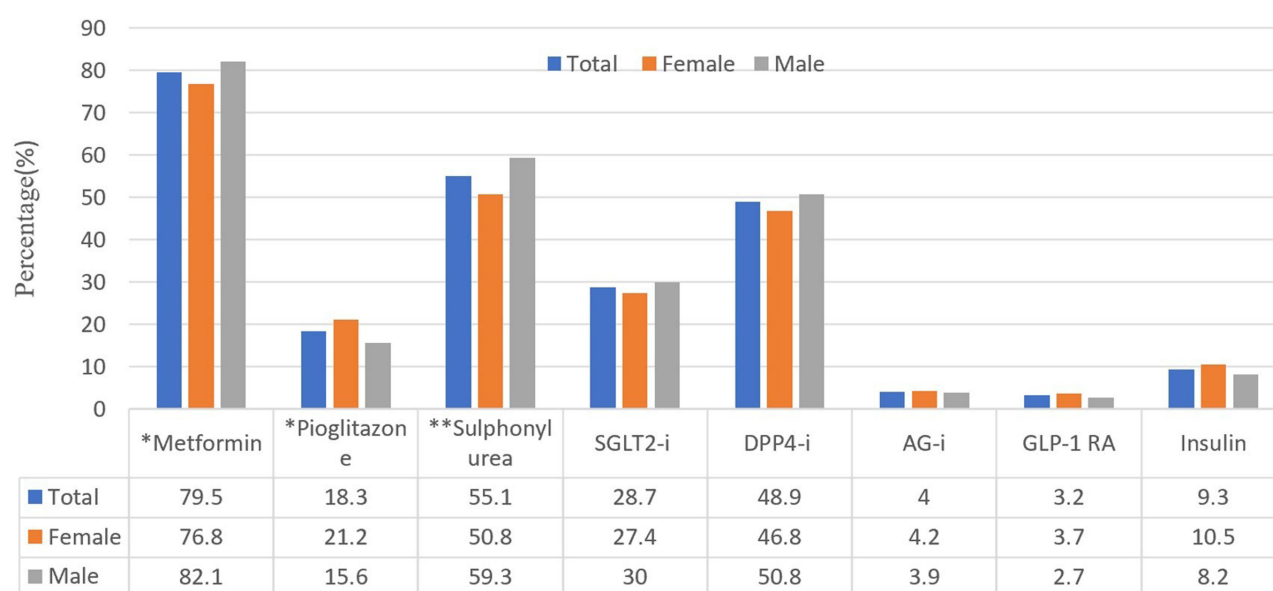


Figure 1 The proportion of antidiabetic medications used by females and males, showing that the use of metformin and sulphonylurea was significantly higher in the male group (76.8% vs 82.1%; $p=0.044$ and 50.8% vs 59.3%; $p=0.009$, respectively); On the other hand, the use of pioglitazone was significantly higher in the female group (21.2% vs 15.6%; $p=0.027$). * $p<0.05$, ** $p<0.01$.

Table 2 Anthropometric and Biochemical Data of 943 Patients with Type 2 Diabetes Were Analyzed Before and After the Lockdown

	Before Lockdown	After Lockdown	P value
BMI (kg/m ²)	26.5 ± 4.5	26.4 ± 4.5	0.624
Weight (kg)	71.2 ± 15.2	70.9 ± 15.1	0.706
Systolic BP (mmHg)	134.5 ± 15.4	134.7 ± 15.2	0.799
Diastolic BP (mmHg)	75.7 ± 11.0	75.7 ± 10.9	0.957
HbA1c (%)	7.0 ± 1.0	6.8 ± 0.9	<0.001*
Proportion of individuals achieving HbA1c target ≤7%	580 (61.5%)	650 (68.9%)	<0.001*
FBG (mg/dL)	132.2 ± 33.3	124.4 ± 30.0	<0.001*
TC (mg/dL)	171.0 ± 34.7	170.6 ± 34.9	0.813
TG (mg/dL)	150.2 ± 117.2	149.1 ± 149.5	0.865
HDL-C (mg/dL)	49.3 ± 13.0	50.1 ± 13.5	0.194
LDL-C (mg/dL)	98.6 ± 28.4	99.1 ± 28.7	0.728
Cr (mg/dL)	0.88 ± 0.31	0.90 ± 0.34	0.191
eGFR (mL/min/1.73 m ²)	89.8 ± 24.3	88.0 ± 24.7	0.098
S-GPT (IU/L)	23.2 ± 13.9	23.4 ± 14.5	0.860
uACR (ug/mg)	85.0 ± 307.2	92.3 ± 332.5	0.620

Note: Values are presented as mean ± standard deviation or number (%). *A p-value less than 0.05 was considered statistically significant.

Abbreviations: HbA1c, glycated hemoglobin; BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Cr, creatinine; S-GPT, serum glutamate pyruvate transaminase; eGFR, estimated glomerular filtration rate; uACR, urine albumin-creatinine ratio.

lockdown compared to the period before the lockdown for both females and males (62.1% vs 70.5%, $p=0.008$; 60.9% vs 67.5%, $p=0.032$, respectively).

Table 3 presents the result of a stepwise multiple regression analysis that was conducted to identify the independent determinants of changes (before-after) in HbA1c levels. The analysis included baseline characteristics and laboratory parameters as variables. After adjusting for age and gender, the analysis revealed that the baseline HbA1c levels before the lockdown were a positive contributor to changes in HbA1c (standardized coefficient +0.16, $p<0.001$). Conversely, BMI and co-morbidity with dyslipidemia were negative contributors to changes in HbA1c levels (standardized coefficient -0.07, $p=0.025$; -0.12, $p=0.001$, respectively).

Discussion

During the COVID-19 pandemic, the national lockdown had a significant impact on healthcare systems and diabetes management. The results of relevant studies were inconsistent. Our study noted that the mean HbA1c levels and FBG were significantly improved after the lockdown, and the proportion of patients achieving HbA1c target was higher. These findings suggested that the lockdown measures had a positive impact on diabetes management in Northern Taiwan as a single-center experience, where the pandemic had been relatively well-controlled. According to the key findings in our study, it contributed to the growing body of literature and provided valuable insights into how even mild or moderate lockdown measures may affect diabetes control among patients with type 2 diabetes, and how this may vary across different populations.

The changes in living behaviors of patients with T2D caused by COVID-19 pandemic varied in different communities, but during COVID-19 lockdown most diabetic patients preferred to cook meals at home and use less takeout, fast

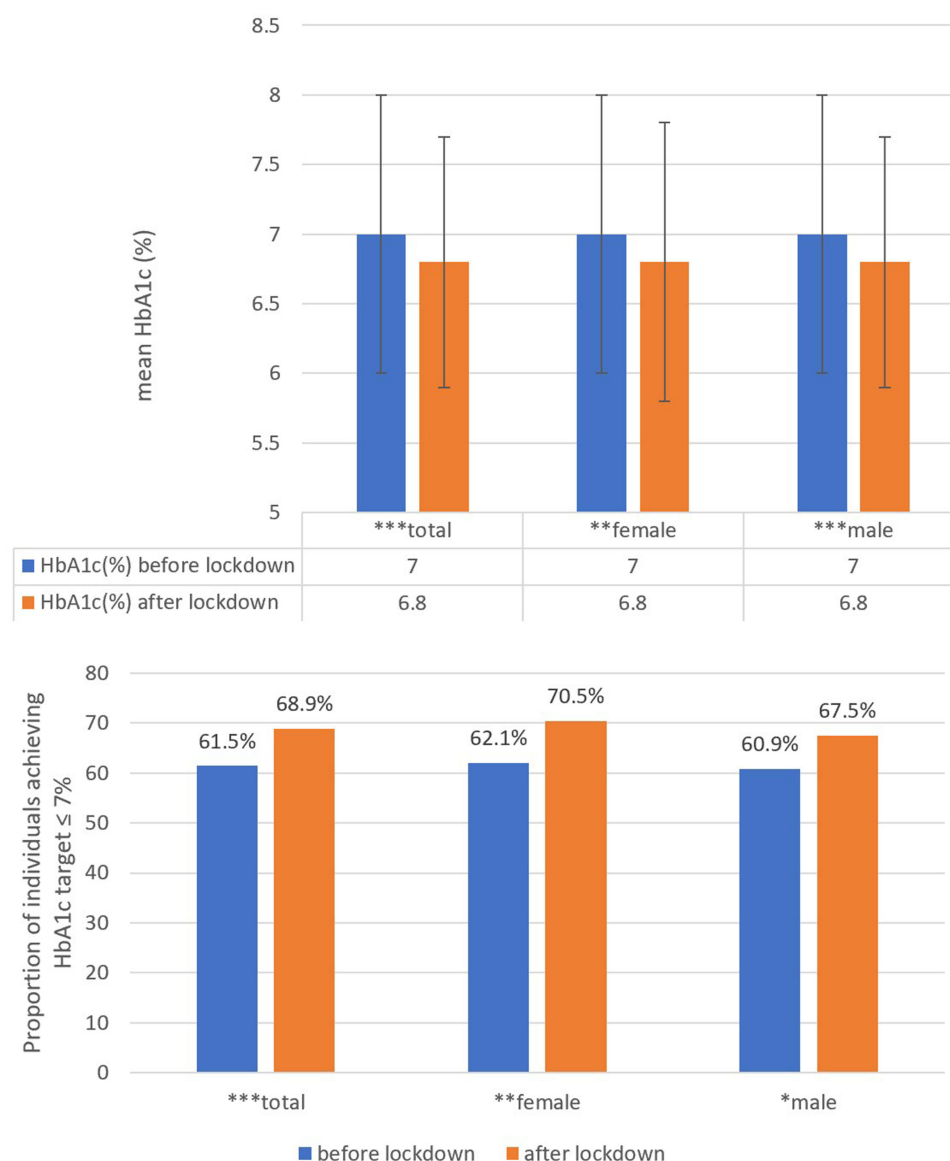


Figure 2 The mean HbA1c was significantly improved in both females and males after the lockdown compared to the period before the lockdown (7.0 ± 1.0 vs 6.8 ± 1.0 , $p=0.004$; 7.0 ± 1.0 vs 6.8 ± 0.9 , $p<0.001$, respectively). Similarly, the proportion of individuals achieving HbA1c target $\leq 7\%$ was significantly higher after the lockdown compared to the period before the lockdown for both females and males (62.1% vs 70.5% , $p=0.008$; 60.9% vs 67.5% , $p=0.032$, respectively). * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

foods, and alcoholic drinks.^{15,16} Although the patients mostly improved their eating habits, the glycemic and anthropometric indices were contradictory in different studies.^{17–21} Moreover, it is well-known that diabetes is a chronic progressive disease that patients require ongoing healthcare management and persistent monitoring for complications over time. The pandemic and its lockdowns mostly influenced routine healthcare resources all over the world, which challenged diabetes management for several reasons, such as reduced utilization of outpatient and inpatient healthcare services, staff and medicine shortages, delayed care seeking, and transport difficulties, etc. All of these difficulties may potentially worsen diabetic control.^{22,23}

In recent, a retrospective cohort study focused on the impact of COVID-19 lockdown in patients with T2D in the middle area of Taiwan also revealed significant HbA1c improvement during or after the lockdown (7.17 ± 1.29 vs 7.03 ± 1.22 , $p<0.001$) with the conclusion of that HbA1c level did not deteriorate after a lockdown measure during the COVID-19 pandemic in Taiwan.²⁴ There may be several reasons why the results of our and their studies in Taiwan differed from those in other regions or countries. Firstly, it is important to note that the impact of COVID-19 lockdowns on glycemic control can vary depending on factors such as

Table 3 Stepwise Multiple Regression Analysis of Changes (Before-After) in HbA1c Levels. After Adjusting for Age and Gender, the HbA1c Levels Before the Lockdown Were a Positive Contributor to Changes in HbA1c Levels. Conversely, BMI and Co-Morbidity with Dyslipidemia Were Negative Contributors to Changes in HbA1c Levels

Variable	Coefficient	95% CI	Standardized Coefficient	P-value
HbA1c before the lockdown	+0.16	0.11 to 0.21	+0.16	<0.001*
BMI	-0.06	-0.12 to -0.01	-0.07	0.025*
Dyslipidemia	-0.12	-0.19 to -0.05	-0.12	0.001*

Note: *A p-value less than 0.05 was considered statistically significant.

Abbreviations: HbA1c, glycated hemoglobin; BMI, body mass index; CI, confidence interval.

the severity of lockdown measures, the duration of the lockdown, and the level of compliance with public health measures. In Taiwan, the government implemented early and effective public health measures, including aggressive contact tracing, wide-spread testing, and quarantine of suspected cases, which helped to limit the spread of COVID-19, shortening the lockdown period, and then minimizing disruptions to daily routines. Secondly, during the lockdown, it was known that Taiwan had a well-developed healthcare system with high levels of access and capacity to healthcare services, including diabetes care. This helped patients with diabetes in Taiwan to maintain optimal glycemic control during this period.³ These reasons could provide practical recommendations for healthcare providers and institutions to add a policy or strategic plan to apply for diabetes patients during the pandemic.

Our study also provided important information on the use of antidiabetic medications on gender differences among patients with T2D in Taiwan, which had not been extensively studied in relevant research. The use of metformin and sulphonylurea was found to be significantly higher in male patients, while pioglitazone was more commonly prescribed to female patients. Some reports suggested that women were usually prescribed lower metformin doses compared to men and reported more gastrointestinal side effects.²⁵ While metformin was considered to have more beneficial effects on myocardial fatty acid and glucose metabolism in men compared with women, thiazolidinedione (pioglitazone) was suggested to be more effective in women compared with men.²⁶ Sulphonylurea may have more HbA1c reduction using in men but no significantly gender-specific differences in the previous study.²⁷ It is important to note that the distribution of anti-diabetic medications can be influenced by a range of factors, including patient characteristics, physician preferences, and healthcare policies.

The result of the stepwise multiple regression analysis is also informative. It is noteworthy that the baseline HbA1c levels before the lockdown were a positive contributor to changes in HbA1c after the lockdown, indicating that patients with higher HbA1c levels before the lockdown may have benefited more from the lockdown measures. The negative contribution of BMI and co-morbidity with dyslipidemia to changes in HbA1c after the lockdown suggests that these factors may have hindered diabetes management during the lockdown period. The results may help public health authorities to make better recommendations to improve glycemic control in these specialized populations.

Limitations

There are several limitations to the study that should be acknowledged. Firstly, it was a retrospective chart review study conducted in a single center in Northern Taiwan, which may limit the generalizability of the findings to other settings and populations. It is subject to biases and limitations inherent in this type of study design, such as selection bias, information bias, and confounding. Secondly, the study evaluated the impact of lockdown measures on diabetes control over a relatively short lockdown period of two months, which may not be sufficient to fully influence the long-term effects of the pandemic on diabetes management and diabetes-related outcomes, such as quality of life, mental health, and diabetes-related complications. Finally, the study only included patients with type 2 diabetes, which limits the generalizability of the findings to other types of diabetes or the general population. There was not enough information from the chart review mentioning lifestyle changes and changes in diabetic drug prescriptions before and after the lockdown. Further research is needed to better understand the specific factors that contribute to changes in glycemic control during lockdown periods and extend the findings of this study in greater detail.

Conclusions

Overall, the study highlights the potential benefits of lockdown measures on diabetes management in Northern Taiwan as a single-center experience with the improvement of HbA1c and fasting blood glucose, which contributes to the growing body of literature on the impact of COVID-19 on diabetes control and management. Understanding these consequences of national lockdown among diabetic patients can help healthcare providers and policymakers to improve diabetes care during the pandemic.

Abbreviations

SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; T2D, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycated hemoglobin; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Cr, creatinine; S-GPT, serum glutamate pyruvate transaminase; uACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.

Ethics Approval and Informed Consent

1. Conflict of interest: All authors declare no conflict of interest.
2. Informed Consent Statement: Informed consent was obtained from the patients included in the study.
3. This study was conducted under the Declaration of Helsinki and was approved by the Institutional Review Board of Taiwan Adventist Hospital, Taipei, Taiwan (approval number: 111-E-07).
4. Approval date of Registry and the Registration No. of the study/trial: N/A.
5. Animal Studies: N/A.

Consent for Publication

All authors confirm that the details of any images, videos, recordings, etc can be published, and that the person(s) providing consent have been shown the article contents to be published.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest.

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