No Worsening of Glycemic Control in Patients with Type 2 Diabetes Mellitus for Three Years during COVID-19 Pandemic Restrictions in Japan

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Objective : To investigate whether the restrictions imposed during the COVID-19 pandemic influenced glycemic control in patients with type 2 diabetes mellitus (2DM) in Japan.

Methods : We conducted a retrospective cohort study. Data was obtained from 351 outpatients with 2DM who visited a single center from January 2019 to September 2023. Changes to random plasma glucose (RPG) and hemoglobin A1c (HbA1c) levels, and the number of hypoglycemic agents (prescriptions)/patients were analyzed. Seasonal changes (first quarter vs. third quarter of the year), gender (female vs. male), and ages (～64 years, 65-74 years and 75 years～) were considered as factors for glycemic control.

Results : RPGs and HbA1cs levels did not significantly increase in a time-dependent manner during the study period, as previously reported. However, seasonal changes, gender differences, and age-dependent differences were observed to be significant ($p<0.05$) factors for glycemic control. The number of hypoglycemic agents, including metformin, SGLT-2 antagonists, and GLP-1 agonists, increased yearly ($p<0.001$).

Conclusion : The absence of a time-dependent worsening of glycemic control in patients with 2DM during the COVID-19 pandemic in Japan may be related psycho-social effects mediated by restrictions that were in place. Additionally improvements adherence to anti-glycemic medications may have been present. *Shinshu Med J 73 : 79―88, 2025*

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Key words : COVID-19, social restrictions, glycemic control

I Introduction

Coronavirus disease 2019 (COVID-19) was declared a public health emergency of international concern in January 2020[1)2)]. In Japan, a nationwide state of emergency was declared on April 7, 2020 and lasted for three years, until May 7, 2023, with periodic relaxation of restrictions during the period. The state of emergency in Japan entailed less strict restrictions in contrast to the lockdowns in Europe[3)4)]. People were requested to stay at home, with restrictions placed on the use of public transportation and facilities. The COVID-19 pandemic had global influences, and affected glycemic control in patients with diabetes mellitus. Some reports have shown altered lifestyles and metabolic influences in patients with diabetes for two months following the declaration of the COVID-19 pandemic[5)-8)], and others showed negative effects on glycemic control and lipid control during a one-year observation period[9)10)]. Thus, we investigated how the three-year voluntary-based restrictions of the COVID-19 pandemic influenced glycemic control in patients with type 2 diabetes mellitus (2DM).

We previously observed worsening random plasma glucose (RPG) and hemoglobin A1c (HbA1c) levels in patients with diabetes mellitus with consistent ten-year outpatient follow-up[11)]. In addition to adherence[12)] glycemic control is also influenced by several factors,

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Table 1 Participant characteristics by the two seasons, first and third quarter of the year. Patients with diabetes were enrolled from 2019 to 2023.

Glycemia	2019	2020	2021	2022	2023
(mg/dl)					
RPG (1st)	168.1 ± 64.7	166.9 ± 65.4	169.3 ± 64.0	166.9 ± 57.7	171.4 ± 64.9 ns #
RPG (3rd)	161.3 ± 54.4	157.0 ± 53.0	159.1 ± 52.9	159.4 ± 59.1	158.0 ± 56.4
(%)					
HbA1c (1st)	7.25 ± 0.94	7.22 ± 0.89	7.29 ± 0.95	7.29 ± 0.99	7.26 ± 0.95 ns NS
HbA1c (3rd)	7.18 ± 0.78	7.17 ± 0.87	7.20 ± 0.88	7.13 ± 0.98	7.15 ± 0.89
No. of drugs (1-3)	1.8 ± 1.3	1.9 ± 1.4	2.0 ± 1.4	2.1 ± 1.4	2.2 ± 1.5 *** NS
No. of drugs (7-9)	1.9 ± 1.3	1.9 ± 1.4	2.1 ± 1.4	2.1 ± 1.4	2.2 ± 1.4

Data between two seasons, 1st quarter and 3rd quarter during each year from 2019-2023 were analyzed by two-way analysis of variance. Between groups comparison was made by Bonferroni test.
ns not significant, * $p<0.05$, ** $p<0.01$, *** $p<0.001$ in 2019, 2020, 2021, 2022 and 2023. NS not significant, # $p<0.05$, ## $p<0.01$, ### $p<0.001$ between two seasons, 1st and 3rd quarter of the year. Interaction was not shown because the interaction between years and seasons was not significant in each data.

including seasonal climate changes[13)-16)], and gender and age[17)-21)]. Worse glycemic control has been reported during the winter season, compared to summer[13)-15)] and these differences are influenced by seasonal events[15)]. Gender and age differences in glycemic control have also been reported, with a superior glucose tolerance observed in younger Japanese females, but attenuated middle-aged females, and the differences were due to the higher insulin secretion potential and lower body mass index (BMI) in younger females[21)].

In the present study, we also investigated whether the three-year restrictions of the COVID-19 pandemic influenced glycemic control mediated by season (first quarter and third quarter of the year), gender (female and male), and age differences (patients <65 years, 65-74 years and ≥ 75 years).

Ⅱ Methods

A Study design

This single-center retrospective observational study was conducted at Shiojiri Kyoritsu Hospital (Shiojiri City, Japan). To determine the influence of the COVID-19 pandemic, we defined the period before the state of emergency as January 1, 2019, to December 31, 2019 (period before the emergency), and the period of the emergency as April 1, 2020, and March 31, 2023. The period between January 1, 2020, and March 31, 2020, was the transient period of emergency in Japan, and the period between July 1, 2023, and September 30, 2023 was after the restrictions of the COVID-19 pandemic state of emergency. During the state of emergency, people were requested to stay at home, and the use of public transportation and facilities was restricted. This study has been done by the medical care protocol as the protocol reported before[11)]. The study protocol was approved by the ethics committee of Shiojiri Kyoritsu Hospital and conformed to the principles of the Declaration of Helsinki.

B Study population

Diabetes was diagnosed based on the Japanese Clinical Practice Guideline for Diabetes[12)]. Patients with 2DM who visited our hospital at least twice from January 1 to March 31 (first quarter of the year) and from July 1 to September 30 (third quarter of the year) in each study year from January 1, 2019, to September 30, 2023 **(Table 1)** were enrolled.

C Data collection and measurements

Extracted data from the electronic charts included gender, age (years), RPG (mg/dl), HbA1c (%), and information on prescribed drugs. Information on the prescription included the classes and doses of oral hypoglycemic agents and the insulin preparations and doses.

D Statistical analysis

The data are shown as mean ± SD. An analysis of variance (one-way or two-way mixed model) was

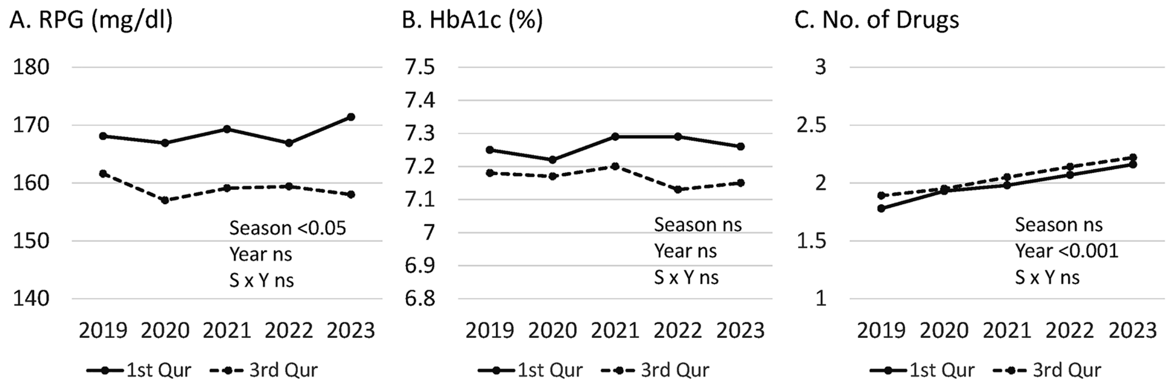

Fig. 1 Characteristics of patients with diabetes from 2019 to 2023 in the first and third quarter of the year. A : RPG (mg/dl), B : HbA1c (%), and C : No. of drugs present, mean changes in blood glucose at any time, mean changes in HbA1c (%), and mean number of drugs prescribed, respectively, in patients with diabetes from 2019 to 2023. Standard deviations (Table 1) were not shown. S (season) x Y (year) indicated the interaction. ns shows not significant.

used for the multiple comparisons, and the Bonferroni test was used for comparison between the two groups if necessary. P values of less than .05 were considered statistically significant.

Ⅲ Results

A Characteristics of the patients registered in 2019

We identified 351 eligible patients with 2DM who had follow-up during the first and third quarters of the year from January 1, 2019, to September 30, 2023. The age at first quarter (mean ± SD) was 69.3 ± 10.7 years old. There were 163 (46.4 %) females and 188 (53.6 %) males. In 2019, there were 91 (25.9 %), 145 (41.3 %) and 115 (32.8 %) patients aged <65 years, 65-74 years, and >74 years, respectively.

B Changes in glycemic control during COVID-19 pandemic restrictions for three years

1 Seasonal differences

The RPG during the first quarter was worse than that of the third quarter ($P<0.05$), but the RPGs of the first and third quarters did not significantly change over the 5 year period. The RPGs during the three-year COVD-19 pandemic period were not worse than the RPG in 2019 **(Table 1, Fig. 1A)**. HbA1cs of the third quarter tended to be less than those of the first quarter but this was not statistically significant **(Table 1, Fig. 1B)**. However, HbA1cs of the first and third quarters did not change during the three-year COVID-19 pandemic period. The numbers of drugs prescribed to patients with 2DM in each quarter increased annually throughout the five-year period ($p<0.001$, **Table 1**, **Fig. 1C**). In contrast, the proportion of the patients receiving non-pharmacological treatment decreased over the five years from 17.4 % in 2019 to 13.7 % in 2023. The proportion of patients with 2DM treated with insulin increased ($p<0.01$, **Table 2**). Additionally, for oral agents, treatment with metformin, sodium glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 agonists (GLP-1a) increased ($p<0.01$). In contrast, treatment with sulphonylureas (SU), alpha-glucosidase inhibitor (α-Gi) and dipeptidyl peptidase-IV inhibitor (DPP-4i) did not change during the period.

When we analyzed the data of RPG and HbA1c for five years in each of the two seasons of the first and third quarters, we observed significant seasonal differences between the first and third quarters for RPG and HbA1c levels ($p<0.05$). Therefore, we analyzed the data from the first quarter and data from the third quarter separately, excluding seasonal effects.

2 Gender differences

In the present study, 46 % (163 of 351) of patients were female and 54 % (188 of 351) were male. The RPG of female patients with 2DM was less than that of the male patients with 2DM in the first ($p<0.001$) and third ($P<0.05$) quarters, but did not significantly

Table 2 Characteristics of patients with diabetes treated successively in the 3rd quarter of the year from 2019-2023.

	2019	2020	2021	2022	2023
Treatment (%)					
Insulin	13.1 ± 33.8	13.1 ± 33.8	13.7 ± 34.4	14.5 ± 35.3	14.8 ± 35.6**
SU	41.2 ± 49.4	41.3 ± 49.3	40.7 ± 49.2	40.2 ± 49.1	39.9 ± 49.0ns
Metformin	32.5 ± 46.9	34.5 ± 7.6	40.2 ± 9.1	44.4 ± 49.8	48.4 ± 50.0***
α-Gi	12.3 ± 56.0	9.7 ± 29.6	10.0 ± 30.0	10.3 ± 30.4	10.0 ± 30.0ns
Pioglitazone	6.6 ± 24.8	6.6 ± 24.8	6.8 ± 5.3	8.0 ± 27.1	7.7 ± 2.7*
DPP-4i	63.5 ± 48.2	64.1 ± 48.0	63.5 ± 48.2	61.3 ± 48.8	61.5 ± 48.7ns
SGLT-2i	21.9 ± 41.4	25.4 ± 43.6	28.8 ± 45.3	31.3 ± 46.5	34.2 ± 47.5***
GLP-1a	0	0	0.6 ± 7.5	3.4 ± 18.2	5.4 ± 23.9***

Data in each year were analyzed using a one-way analysis of variance. Comparisons between the groups were performed using the Bonferroni test.
ns not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
SU : sulphonylureas, α-Gi : alpha-glucosidase inhibitor, DPP-4i : dipeptidyl peptidase-IV inhibitor, SGLT-2i : sodium glucose cotransporter-2 inhibitor, GLP-1a : glucagon-like peptide-1 agonist.

change over five years. RPGs were not higher during the COVID-19 pandemic three-year period compared to the period before COVID-19 restrictions were enforced **(Table 3, Fig. 2A)**. HbA1cs were lower in females ($p < 0.05$, **Fig. 2B**) in the first and third quarters of the year. However, HbA1cs of females and males did not change during the COVID-19 pandemic three-year although the HbA1cs of female in the third quarter was less, but not significant, than the HbA1c of female in 2019. The number of drugs prescribed for female patients with 2DM increased annually over five year period ($p < 0.001$, **Table3**, **Fig. 2C**), but the increase was less than that for male patients ($p < 0.05$).

3 Age differences

To clarify the effects of the restrictions of the COVID-19 pandemic over three years on the age-dependent differences in glycemic control of patients with 2DM, patients were grouped by age, G1 : 64 years or younger ; G2 : 65-74 years ; and G3 : 75 years or older **(Table 4)**.

The RPGs in the first and third quarters were different for each group. The RPGs of G3 was higher than those of G1 and G2 ($P < 0.01$), but the RPGs of G1, G2 and G3 did not differ significantly over five years, including the three-year COVID-19 pandemic period **(Fig. 3A)**. HbA1cs in the first and third quarters did not change significantly for five years among the three groups **(Fig. 3B)** and HbA1c tended to be higher in G1, but not significantly, than those of G2 and G3. The number of the drugs prescribed for patients with 2DM in G1, G2 and G3 increased over five years ($p < 0.001$), and the number of drugs in the first or third quarter in G1 was higher ($P < 0.05$) than those of drugs in older age groups G2 and G3 **(Fig. 3C)**. Younger patients were treated with a higher proportion of agents (interaction between years and subgroups was $p < 0.05$).

Ⅳ **Discussion**

In the present study, from April 2020 to May 2023, during the three-year period of voluntary restrictions induced by COVID-19 in Japan, RPGs and HbA1cs did not significantly increase in a time-dependent manner, contradictory to previous reports[11]. Additionally, during the third quarter of the years during the restrictions, the RPGs and HbA1cs for females were less than those in 2019, although these changes did not significantly decrease after the restrictions of the COVID-19 pandemic **(Fig. 2)**. We prescribed drugs for glycemic control in patients with diabetes annually for five years as reported before[11], suggesting good adherence by patients with 2DM, and optimum maintenance over the study period.

Glycemic control might be affected by the adherence as well as the social restriction in place during the COVID-19 pandemic, seasonal changes in tem-

Table 3 Characteristics of female (n = 163) and male (n = 188) patients with diabetes treated successively from 2019 to 2023.

Glycemia	2019	2020	2021	2022	2023
(mg/dl)					
1st quarter					
RPG (female)	157.3 ± 59.4	161.1 ± 68.7	159.4 ± 59.7	156.1 ± 49.7	160.8 ± 61.5 ns ###
RPG (male)	177.6 ± 67.7	171.9 ± 62.2	177.9 ± 66.5	176.3 ± 62.4	180.5 ± 66.5
3rd quarter					
RPG (female)	156.0 ± 50.5	154.6 ± 53.0	153.6 ± 48.3	152.3 ± 57.9	149.2 ± 51.7 ns #
RPG (male)	165.9 ± 57.3	159.0 ± 53.1	163.9 ± 56.2	165.5 ± 59.5	165.7 ± 59.2
(%)					
1st quarter					
HbA1c (female)	7.15 ± 0.81	7.16 ± 0.88	7.17 ± 0.87	7.20 ± 0.82	7.14 ± 0.89 ns #
HbA1c (male)	7.34 ± 1.03	7.27 ± 0.90	7.40 ± 1.00	7.38 ± 1.11	7.34 ± 0.98
3rd quarter					
HbA1c (female)	7.11 ± 0.76	7.10 ± 0.80	7.10 ± 0.75	7.02 ± 01.03	7.09 ± 0.78 ns #
HbA1c (male)	7.24 ± 0.80	7.24 ± 0.92	7.29 ± 0.97	7.22 ± 0.93	7.20 ± 0.97
1st quarter					
No. of drugs (female)	1.7 ± 1.3	1.8 ± 1.4	1.8 ± 1.4	1.9 ± 1.3	1.9 ± 1.54 *** #
No. of drugs (male)	1.9 ± 1.3	2.1 ± 1.3	2.1 ± 1.3	2.3 ± 1.4	2.4 ± 1.5
3rd quarter					
No. of drugs (female)	1.7 ± 1.4	1.7 ± 1.4	1.8 ± 1.4	1.9 ± 1.4	2.0 ± 1.3 *** ##
No. of drugs (male)	2.0 ± 1.3	2.1 ± 1.3	2.2 ± 1.4	2.4 ± 1.4	2.5 ± 1.4

Data for female and male patients with diabetes mellitus were analyzed in 2019, 2020, 2021, 2022, and 2023 using two-way analysis of variance in each season, 1st quarter and 3rd quarter. Comparison between the groups were performed using the Bonferroni test.

ns not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ in 2019, 2020, 2021, 2022 and 2023. NS not significant, #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ between female and male. Interaction was not shown because the interaction between years and gender was not significant in each data.

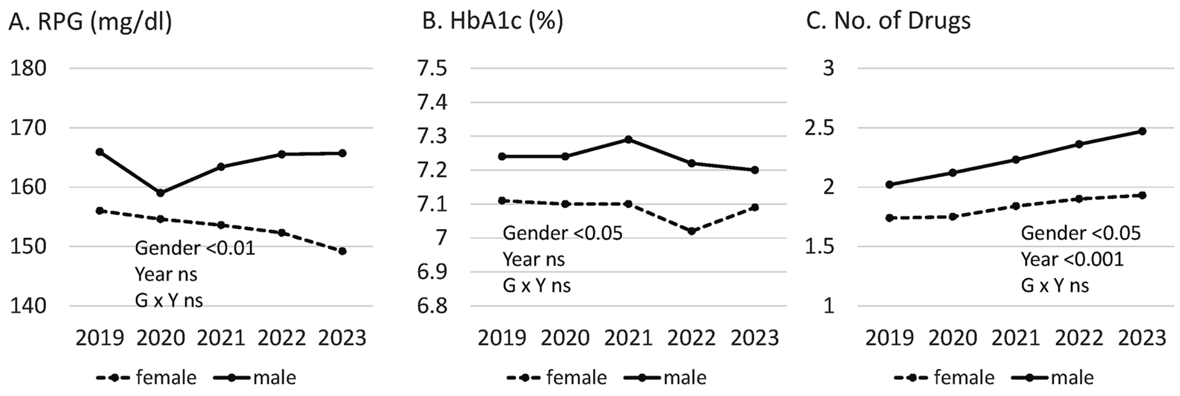

Fig. 2 Gender differences on the effect of glycemic control during the 3rd quarter of the year in patient with diabetes from 2019 to 2023 in 163 female and 188 male ptients.

A : RPG (mg/dl), B : HbA1c (%), and C : No. of drugs present, mean changes in blood glucose at any time, mean changes in HbA1c (%), and mean number of drugs prescribed, respectively. Standard deviations are not shown. G (gender) x Y (year) represents the interaction. ns shows not significant.

Table 4 Characteristics of the three age groups, G1 (<65 years, n = 91 (25.9 %)), G2 (65 years ～74 years, n = 145 (41.3 %)) and G3, (75 years～, n = 115, (32.8 %)) of the patients with diabetes treated successively in 1^{st} and 3^{rd} quarter of the year for 5 years from 2019 to 2023.

Variable	2019	2020	2021	2022	2023
G1 (years old)	55.2 ± 7.9				
G2 (years old)	69.8 ± 2.8				
G3 (years old)	80.0 ± 4.1				
G1 (1st) RPG (mg/dl)	150 ± 96.2	158 ± 70.0	159 ± 54.9	159 ± 60.5	162 ± 61.4$^{ns\ ***}$
G2 (1st) RPG (mg/dl)	169 ± 68.5	160 ± 59.4	163 ± 63.7	161 ± 50.2	167 ± 63.2
G3 (1st) RPG (mg/dl)	182 ± 64.6	182 ± 66.6	185 ± 68.5	181 ± 61.9	185 ± 68.1
G1 (3rd) RPG (mg/dl)	154 ± 60.0	149 ± 56.2	155 ± 64.9	150 ± 54.9	148 ± 58.1$^{ns\ **}$
G2 (3rd) RPG (mg/dl)	159 ± 52.4	157 ± 52.7	154 ± 49.8	153 ± 55.4	155 ± 47.4
G3 (3rd) RPG (mg/dl)	169 ± 70.8	164 ± 50.5	169 ± 55.5	175 ± 63.8	169 ± 63.4
G1 (1st) HbA1c (%)	7.33 ± 1.1	7.30 ± 1.0	7.49 ± 1.1	7.48 ± 1.3	7.41 ± 0.9$^{ns\ NS}$
G2 (1st) HbA1c (%)	7.23 ± 0.9	7.15 ± 0.7	7.21 ± 0.8	7.18 ± 0.8	7.18 ± 0.8
G3 (1st) HbA1c (%)	7.20 ± 0.9	7.23 ± 1.0	7.24 ± 1.0	7.29 ± 1.0	7.26 ± 1.1
G1 (3rd) HbA1c (%)	7.30 ± 1.0	7.32 ± 1.1	7.39 ± 1.0	7.27 ± 0.9	7.24 ± 1.0$^{ns\ NS}$
G2 (3rd) HbA1c (%)	7.11 ± 0.7	7.11 ± 0.7	7.14 ± 0.8	7.04 ± 1.0	7.10 ± 0.7
G3 (3rd) HbA1c (%)	7.17 ± 0.7	7.14 ± 0.8	7.13 ± 0.9	7.11 ± 1.0	7.15 ± 0.9
Treatment (%)					
G1 (1st) No. of drugs	2.1 ± 1.4	2.4 ± 1.4	2.4 ± 1.3	2.6 ± 1.3	2.7 ± 1.4$^{***\#\#\#\$\$}$
G2 (1st) No. of drugs	1.9 ± 1.2	2.0 ± 1.3	2.0 ± 1.4	2.1 ± 1.4	2.2 ± 1.4
G3 (1st) No. of drugs	1.4 ± 1.4	1.5 ± 1.2	1.6 ± 1.3	1.6 ± 1.3	1.7 ± 1.4
G1 (3rd) No. of drugs	2.3 ± 1.4	2.4 ± 1.3	2.5 ± 1.3	2.7 ± 1.4	2.8 ± 1.4$^{***\ \#\#\#\$}$
G2 (3rd) No. of drugs	2.0 ± 1.3	2.0 ± 1.4	2.1 ± 1.4	2.2 ± 1.4	2.2 ± 1.4
G3 (3rd) No. of drugs	1.5 ± 1.2	1.5 ± 1.2	1.6 ± 1.3	1.7 ± 1.4	1.7 ± 1.4

Data from three age groups, G1, G2 and G3 patients with diabetes mellitus, and data from 2019, 2020, 2021, 2022, and 2023 as factors were analyzed using two-way analysis of variance in each season, 1^{st} quarter and 3^{rd} quarter. Comparisons between the groups were performed using the Bonferroni test.
ns not significant, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ in 2019, 2020, 2021, 2022 and 2023. NS not significant, $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ among three groups. $^{\$}p<0.05$, $^{\$\$}p<0.01$ interaction (GxY) between years (Y) and ages groups (G).

perature or events, gender, and/or age, for example, duration of diabetes and aging. We confirmed seasonal changes **(Table 2, Fig. 1)** as reported that glycemic control in the first quarter of the year was worse than that in the third quarter of the year[10)13)-16)]. However, the restrictions of the COVID-19 pandemic did not worsen glycemic control in patients with 2DM in the present study, although previous reports suggested worse glycemic control for one year after the COVID-19 pandemic[10)]. On the other hand, glycemic control of the patients with type 1 diabetes mellitus was not worse than that of control before COVID-19 pandemic[10)] as a result of maintaining regular follow-up. During the COVID-19 lockdown, glycemic control in patients with type 1 diabetes mellitus significantly improved[22)]. Thus, our patients with 2DM have been maintaining their adherence, that is, regular follow-up, RPG and HbA1c levels during treatments, increases in the number of the agents, including metformin, SGLT-2 inhibitors and GLP-1 agonists **(Table 2)**, and continued discussion with medical stuffs[11)].

Glycemic control was worse in winter than that in summer[13)-15)]. Seasonal differences are influenced by weather and seasonal events[14)]. For one year in Japan, glycemic control in people with diabetes mellitus during the restrictions of the COVID-19 pandemic

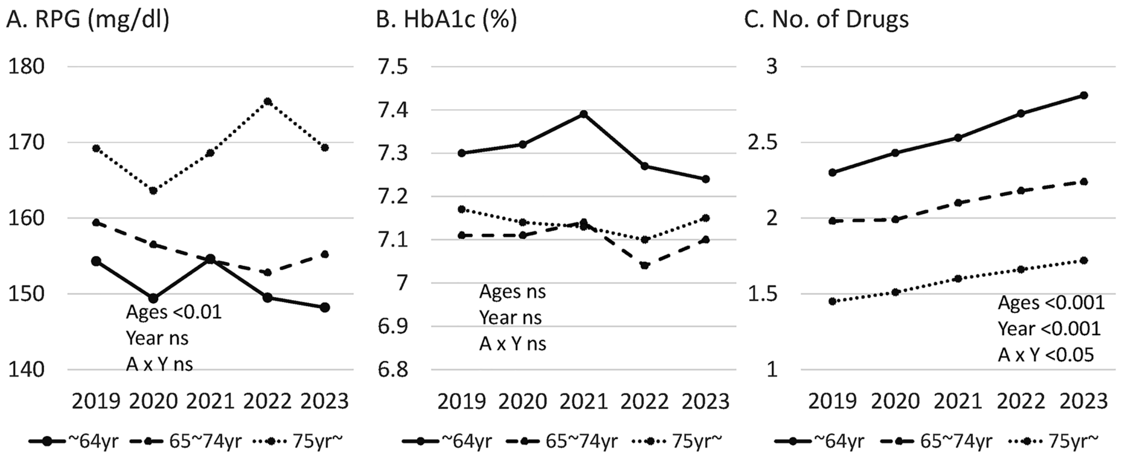

Fig. 3 Changes in the characteristics of patients with diabetes among three age groups, <65 years (solid line), 65 years ~74 years (broken line), and ≥ 75 years (dotted line) over 5 years.
A : RPG (mg/dl), B : HbA1c (%), and C : No. of drugs present mean changes in blood glucose at any time, mean changes in HbA1c (%), and mean number of drugs prescribed, respectively. Standard deviations are not shown. A (age) x Y (year) represents the interaction.
Medication adherence is defined by the World Health Organization as "the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider.
We also did not determined the direct effects of COVID-19 infection on the patients registered in the present study who were not determined, although the registered patients visited our hospital regularly for 5 years even if they would been suffered from COVID-19. We could not determine exactly the COVID-19 infectious state in the present study.

was worse than that before the COVID-19 pandemic in summer and winter[10]. However, in our study, glycemic control in winter was worse than that in summer but no significant differences were observed before, during, or after the restrictions of the COVID-19 pandemic were in place. Additionally, HbA1cs levels in the first quarter of the year (from January to March) and the third quarter of the year, (from July to September) did not change significantly in the present study. These results suggest that the restriction of the winter events, for example, Christmas and New Year's Day, during the COVID-19 pandemic might have affected the glycemic control of patients with diabetes mellitus in our study.

Although the glycemic control of the younger female patients with 2DM in Southern Europe was worse than that of the male[18)19)], the superior glucose tolerance in Japanese females was apparent at younger ages, but this effect was attenuated in middle-aged females, and the differences were due to the higher insulin secretion potentials and lower body mass index (BMI) in young females[21]. In the younger patients with 2DM, emotional support and age were significant positive predictors of Summary of Diabetes Self-Care Activities Measure (SDSCA) in male and interdependent tendency was a significant negative predictor in female[20]. In the present study, the glycemic control (RPG and HA1c) of female patients with 2DM was better than that of male patients, although the number of hypoglycemic agents per patient was lower in female patients than in male patients. Glycemic control in both female and male patients with 2DM did not worsen during the COVID-19 pandemic. However, before the COVID-19 pandemic the RPGs of the female patients with diabetes mellitus were lower than those of the male patients, and the RPGs increased significantly for 10 years from 2009 to 2019. HbA1cs of female patients did not change, but that of male patients increased significantly for 10 years (unpublished data)[11]. We employed newly developed agents, including SGLT-2i and GLP-1a, over the last 15 years from 2009 to 2023. Therefore, we suggest that the lack of significant time-dependent changes in glycemic control during the restrictions of the

COVID-19 pandemic might be caused by the additional effects, for example, psycho-social effects, in addition to the improvement of adherence to glycemic control.

The glycemic controls of the three age groups did not change during the restrictions of the COVID-19 pandemic, and there was no age differences in HbA1cs among the three groups, although the number of hypoglycemic agents increased with time and the increases was greater in patients under 65 years of age **(Table 4, Fig. 3)**. We previously reported that the glycemic control, RPGs and HbA1cs of 168 patients with diabetes mellitus worsened in a time-dependent manner, and that the RPGs of patients over 75 years of age were higher than those of patients under 65[11], a similar to the findings of the present study. Time- and age-dependent worsening of glycemic control might be induced by deterioration of the glycemic control system in as a result of advanced age[12][23]. Thus, the government's announcement that diabetes mellitus is associated with mortality, sever COVID-19, ARDS, and disease progression in patients with COVID-19[24][25] may affect the psychosocial effects of maintaining better glycemic control in adult and older patients with 2DM. Therefore, absence of a time-dependent worsening effects to glycemic control in patients with 2DM during the voluntary-based restrictions of the COVID-19 pandemic in Japan suggests that additional effects, such as psychosocial effects, mediated by the restrictions of the COVID-19 pandemeic, affected glycemic control and improved adherence to anti-glycemic agents.

The retrospective nature of the study imposes many limitations to the findings. The treatment strategies were not consistent, despite systemic health-care efforts improve the health of patients with diabetes. Importantly, the treatment targets were not predetermined between four doctors mainly responsible for the management of the patients with diabetes. Medical social workers are also involved in financial and daily life issues. Additionally, data regarding diabetic complications were not available. Further, our study was conducted at a single center, and the results may not be representative of the general Japanese population with 2DM. We did not determined the direct effects of COVID-19 on the patients registered in the present study, although the registered patients had regular follow-up over the five year period, even if they had COVID-19. Furthermore, we could not determine the severity of COVID-19 infections in the present study. Despite these limitations, we believe that this paper describes the important aspects of the three-year-long effects of COVID-19 pandemic restrictions on glycemic control in patients with diabetes in Japan.

V Conflict of Interests

None.

Acknowledgement

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Compliance with Ethical Standards

The project was studied with humans but it is retrospective, and was approved by the ethics committee of Shiojiri Kyoritsu Hospital.

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