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Impact of the first announced state of emergency owing to coronavirus disease 2019 on stress and blood pressure levels among patients with type 2 diabetes mellitus in Japan

Shun Ito[1†], Kazuo Kobayashi[1,2*†], Keiichi Chin[1], Shinichi Umezawa[1], Hareaki Yamamoto[1], Shiro Nakano[1], Nobukazu Takada[1], Nobuo Hatori[3], Kouichi Tamura[2]

[1]Sagamihara Physicians Association, Sagamihara, Japan, [2]Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan, and [3]Department of Cardiology, Kobayashi Hospital, Odawara, Japan

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***Correspondence**
Kazuo Kobayashi
Tel.: +81-4275-53311
Fax: +81-4277-07372
E-mail address:
k-taishi@xc4.so-net.ne.jp

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ABSTRACT

Aims/Introduction: After the first coronavirus disease 2019 state of emergency announcement, there was an increase in stress that might have affected the self-management of patients with type 2 diabetes mellitus. This study identified the changes in clinical findings and stress among patients with type 2 diabetes mellitus, and investigated the characteristics of patients who experienced an increase in blood pressure (BP) after the announcement.

Materials and Methods: Retrospectively, we scrutinized 310 patients with type 2 diabetes mellitus who were treated by the Sagamihara Physicians Association. After the announcement, 164 and 146 patients showed an increase (ΔBP >0 group) and decrease in BP (ΔBP $\leq$0 group), respectively. The propensity score matching method was used to compare the differences in clinical findings and stress-related questionnaire responses between the two groups.

Results: After the announcement, 47% of patients experienced an increase in daily stress. Furthermore, 17% and 36% reported worsening dietary intake and a decrease in exercise, respectively. More patients reported that their dietary and salt intake had worsened in the ΔBP >0 group than in the ΔBP $\leq$0 group (9% vs 20%, $P = 0.02$, and 3% vs 10%, $P = 0.04$, respectively). Additionally, both systolic and diastolic BP measured in the office were significantly increased ($P = 0.02$ and $P = 0.03$, respectively); however, systolic BP measured at home significantly decreased ($P = 0.01$). The total stress scores were higher in the ΔBP >0 group than in the ΔBP $\leq$0 group (0.05 ± 2.61 and 0.93 ± 2.70, respectively, $P = 0.03$).

Conclusions: An increase in stress and, particularly, worsening dietary and salt intake were noted among patients with type 2 diabetes mellitus who experienced an increase in BP after the state of emergency announcement.

INTRODUCTION

The World Health Organization declared a global coronavirus disease 2019 (COVID-19) pandemic owing to the spread of severe acute respiratory syndrome coronavirus 2 on 11 March 2020. The government of Japan announced a state of emergency on 7 April 2020 as a precaution for the further spread of COVID-19. By this state of emergency, people were requested to remain in their homes and maintain social distancing to reduce person-to-person contact during daily activities. Accordingly, daily stress was expected to increase, especially among patients with chronic diseases, such as hypertension, diabetes

†These authors contributed equally to this manuscript.
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mellitus or dyslipidemia, whereby the state of emergency would likely affect their diet or exercise interventions. Japan is located in an area where natural disasters, such as typhoons, earthquakes or heavy rains, often occur, and these disasters increase stress and lead to cardiovascular complications among the people in Japan[1–3]. Although the COVID-19 pandemic differed from conventional natural disasters, it is thought that the state of emergency caused increased stress among the people in Japan. We previously reported an increase in blood pressure (BP) after the state of emergency announcement among outpatients who visited clinics in Japan[4]. We also reported that the increase in BP was related to worsening dietary intake.

Diet and exercise interventions can reduce the risk of complications in patients with diabetes mellitus[5]. In a survey carried out in the USA, one-third of the patients had worsening dietary intake, and half experienced a decrease in exercise[6]. The COVID-19 pandemic disrupted both diet and exercise interventions, and became an indirect risk for patients with diabetes mellitus. Furthermore, it has previously been reported that having to maintain social distancing to reduce person-to-person contact might increase the incidence of anxiety and depression, which could lead to poor medication adherence[7]. Patients with diabetes mellitus are considered at increased risk for not only common infections, but also more severe COVID-19 infections[8–10]. This further emphasizes the increased stress among patients with diabetes mellitus during the COVID-19 pandemic. Therefore, the stress caused by the COVID-19 pandemic and the subsequent state of emergency was likely a major concern among patients with diabetes mellitus. Several retrospective studies reported the relationship between the stress caused by the COVID-19 pandemic and the level of hemoglobin A_{1c} (HbA_{1c}) or bodyweight (BW) in Japanese patients with diabetes mellitus[11–18]. Appropriate BP control is also important in the management of patients with diabetes mellitus; however, only one study carried out by Endo *et al.*[19] reported the relationship between stress, dietary intake or exercise and systolic BP and HbA_{1c} in Japanese patients with diabetes mellitus under the state of emergency. Their study was retrospectively carried out at a single center, and other clinical data, including BW, were lacking. Therefore, the present study aimed to evaluate the changes in clinical findings, including BP, HbA_{1c} and BW, and stress among patients with type 2 diabetes mellitus, and investigate the characteristics of patients who experienced an increase in BP after the state of emergency announcement.

MATERIALS AND METHODS

Patients and data collection

The present study was a subanalysis of our previous study[4] and involved the same patients. Retrospectively, we scrutinized 748 patients with chronic diseases who were treated by the Sagamihara Physicians Association to determine changes in stress during the state of emergency due to COVID-19 from 7 April to 31 May 2020. In this subanalysis, we included patients with: (i) type 2 diabetes mellitus; (ii) clinical findings for sex, age, BW, diastolic BP (DBP), systolic BP (SBP), HbA_{1c} levels, serum creatinine levels, estimated glomerular filtration rate (eGFR) and urinary protein levels (urine albumin-to-creatinine ratio [ACR] or qualitative proteinuria) collected both before and after the state of emergency; and (iii) data on the use of concomitant agents (antihypertensive agents, hypoglycemic agents, statins, ezetimibe and antiplatelet agents). Based on these inclusion criteria, 310 out of 748 patients were included in the present study.

BP measurement and clinical data

BP measurement in the office was carried out using validated cuff oscillometric devices during one visit at each institution during the state of emergency. In accordance with the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019)[20], BP measurement in the office was carried out in a quiet setting after allowing the patient to rest for a couple of minutes in a seated position with uncrossed legs. BP measurement at home was also carried out using oscillometric devices with upper arm cuffs in accordance with the JSH 2019 guidelines[20]. At home, the patients carried out BP measurements early every morning, and the average values of the those taken the week immediately before visiting the clinic were calculated. The eGFR was calculated as follows: eGFR ($mL/min/1.73\ m^2$) = $194 \times \text{age} - 0.287 \times \text{serum creatinine} - 1.094 \times (0.739 \text{ for women})$[21].

Regarding the urinary protein levels, the level of the qualitative proteinuria values were transformed to the level of the albuminuria values using the formula reported by Sumida *et al.*,[22] and the resulting logarithmic values were used in the analysis. In some cases, the estimated salt intake was calculated from spot urine samples using Tanaka's formula[23]. Further analyses to compare these two groups were carried out.

Questionnaire investigating changes in stress after the state of emergency announcement

In the present study, we analyzed the responses to a questionnaire investigating changes in stress after the state of emergency announcement. This was described in our previous survey[4]. The questionnaire contained nine questions, including fear of the relationship between COVID-19 and hypertension, daily stress, dietary intake, salt intake, frequency of eating lunch or dinner at home, amount of exercise, amount of alcohol intake, quality of sleep and medication adherence. Furthermore, the answers to the nine questions were changed to discrete variables, scored from −2 to +2 points, and summed to determine the total stress score. This questionnaire was administered as part of our regular clinical practice to help patients care for their medical conditions during the state of emergency. Consequently, patient informed consent was not required.

Multiple linear regression analysis of changes in mean arterial pressure

Multiple linear regression analysis was carried out to evaluate independent predictors of the change in office mean arterial pressure (ΔMAP). The values of MAP were utilized in this study and calculated as "(SBP − DBP)/3 + DBP". We selected covariates that were thought to be confounding factors for changes in BP, such as sex, age, BW before the state-of-emergency announcement, MAP from January to March 2020, eGFR, use of antihypertensive and hypoglycemic drugs, and answers to the nine questions that were converted to discrete variables. Multiple linear regression analysis with a stepwise method was carried out. Additionally, Pearson correlation coefficients were used to analyze the correlation between ΔMAP, ΔBW and ΔHbA_{1c}.

Propensity score matching to compare the changes in BP after the state of emergency announcement between the two groups

Of the 310 patients, 164 experienced an increase in MAP in the office after the state of emergency announcement (ΔBP >0 group), and 146 showed a decrease in BP (ΔBP ≤0 group). Further analyses were carried out to compare the two groups using propensity score (PSs). The PSs of patients in the ΔBP >0 group were calculated using a logistic regression model with continuous variables including age, BW, SBP, DBP, MAP, HbA_{1c}, the logarithmic value of ACR and baseline eGFR, as well as categorical variables including sex and the use of concomitant medications (antihypertensive agents, hypoglycemic agents, statins, ezetimibe and antiplatelet agents).

PS matching was carried out with the following algorithm: 1:1 nearest neighbor matching with a caliper value of 0.05, equal to the width of one-quarter of the standard deviation of the PS without replacement[24]. We compared the changes in clinical characteristics between the two groups using a paired *t*-test for the matched cohort model. For the questionnaire responses, the frequencies of the responses "a little worsening" and "much worsening" were compared using McNemar's test in the matched model.

Statistical analysis

All statistical analyses were carried out using Statistical Package for the Social Sciences software (IBM SPSS version 25.0; IBM Corp., Armonk, NY, USA). Normally distributed data are presented as the mean ± standard deviation, and skewed distributions are presented as the median (lower quartile, upper quartile). For parametric covariates, the differences between two time points were compared using a paired *t*-test; for non-parametric covariates, the Wilcoxon signed-rank test was used. A χ^2-test was carried out to compare differences in categorical data. Differences were considered significant at a *P*-value of <0.05.

RESULTS

Change in clinical findings and stress after the state of emergency announcement

The clinical characteristics of the 310 patients during the COVID-19 state of emergency are shown in Table 1. There was a significant increase in office SBP/DBP/MAP and a significant decrease in home SBP/MAP after the state-of-emergency announcement ($P = 0.02$, 0.03, 0.01, 0.01 and 0.02, respectively; Table 2). However, SBP at home significantly decreased ($P = 0.01$; Table 2). No significant changes in BW, HbA_{1c}, eGFR, ACR and estimated salt intake were noted (Table 2).

Table 1 | Clinical characteristics of 310 cases during the state of emergency due to coronavirus disease 2019

Characteristics of patients	
Male (%)	197 (64%)
Age (years)	68.6 ± 11.3 (range 28–93)
Hypertension	300 (97%)
Dyslipidemia	299 (97%)
Chronic kidney disease	190 (61%)
Cardiovascular disease	74 (24%)
Cerebrovascular disease	25 (8%)
Current medications during the state of emergency	
Antihypertensive agents	
ARB	169 (55%)
ACEI	25 (8%)
Ca channel blocker	146 (47%)
β-Blocker	50 (16%)
Thiazide	13 (4%)
Mineralocorticoid receptor blocker	23 (7%)
Loop diuretic	5 (2%)
Hypoglycemic agents	
DPP4 inhibitor	137 (44%)
Metformin	89 (29%)
SGLT2 inhibitor	63 (20%)
Insulin	48 (16%)
Sulphonyl urea	59 (19%)
GLP-1 receptor agonist	20 (7%)
Pioglitazone	32 (10%)
α-Glucosidase inhibitor	65 (21%)
Glinide	30 (10%)
Others	
Statin	255 (82%)
Ezetimibe	60 (19%)
Antiplatelet	77 (25%)

Data shown are numbers (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter 2.

Table 3 shows the questionnaire answers to the questions related to changes in stress after the state of emergency. Of the patients, 47% reported increased daily stress. More patients indicated "worsened" than "improved" dietary intake, amount of exercise, quality of sleep and medication adherence, and the frequency of the responses of "a little worsened" or "much worsened" were 17, 36, 16 and 5%, respectively.

Multiple linear regression analysis of changes in office MAP and home MAP

A multiple linear regression analysis of changes in MAP measurements was carried out to identify the following independent

Table 2 | Change in clinical findings before and after the announcement of the state of emergency due to coronavirus disease 2019

Total (n = 310)	January to March 2020	During the state of emergency	P-value
BW (kg)	65.0 ± 12.4	64.8 ± 12.5	0.17†
BMI (n = 285)	24.5 ± 3.7	24.4 ± 3.7	0.31†
Office-SBP (mmHg)	139.3 ± 19.0	141.6 ± 18.6	0.02†
Office-DBP (mmHg)	77.5 ± 12.4	78.8 ± 11.9	0.03†
Office-MAP (mmHg)	98.0 ± 12.8	99.7 ± 12.2	0.01†
Pulse rate (n = 285)	80.1 ± 13.8	80.0 ± 13.1	0.85†
Home-SBP (mmHg) (n = 206)	128.6 ± 8.9	127.5 ± 8.9	0.01†
Home-DBP (mmHg) (n = 206)	74.9 ± 8.6	74.4 ± 8.5	0.08†
Home-MAP (mmHg) (n = 206)	92.8 ± 7.6	92.8 ± 7.6	0.02†
eGFR (mL/min/1.73 m^2)	68.9 ± 19.8	68.1 ± 19.3	0.08†
HbA_{1c} (mmol/mol [%])	51.0 ± 10.3 (6.8 ± 0.9)	51.4 ± 10.1 (6.9 ± 0.9)	0.19†
ACR (mg/gCr)	10.1 [4.9–22.9]	9.5 [5.3–24.0]	0.51‡
Logarithmic value of ACR	1.31 ± 0.07	1.25 ± 0.07	0.23†
Estimated sodium intake, g/day (n = 269)	9.4 [7.9–10.8]	9.1 [7.4–10.7]	0.36‡

Data shown as the mean ± standard deviation or median [lower quartile, upper quartile]. †Paired t-test. ‡Wilcoxon signed-rank test. ACR, urine albumin-to-creatinine ratio; BMI, body mass index; BW, body weight; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; MAP, mean arterial pressure; SBP, systolic blood pressure.

Table 3 | Questions related to the change in stress after the state of emergency

Q1. Do you worry about adverse effects of hypertension as a contributing condition to the severity and poor prognosis of COVID-19?

No, never	Yes, a little	Neither yes or no	Yes, moderately	Yes, strongly	No answer
10 (3%)	77 (25%)	17 (5%)	113 (37%)	80 (26%)	13 (4%)

Q2. How did the stress in your daily life change after the announcement of a state of emergency due to the rapid spread of COVID-19?

Much decreased	A little decreased	Usual	A little increased	Much increased	No answer
6 (2%)	11 (4%)	145 (47%)	113 (37%)	32 (10%)	3 (1%)

Q3. How did your lifestyle change after the announcement of a state of due to the rapid spread of COVID-19?

	Much improved	A little improved	Usual	A little worsened	Much worsened	No answer
Dietary intake	7 (2%)	32 (10%)	219 (71%)	49 (16%)	2 (1%)	1 (0%)
Salt intake	8 (3%)	36 (12%)	244 (79%)	20 (7%)	0 (0%)	2 (1%)
The frequency of dinner or lunch at home	25 (8%)	34 (11%)	242 (78%)	7 (2%)	0 (0%)	2 (1%)
Amount of exercise	10 (3%)	33 (11%)	156 (50%)	76 (25%)	35 (11%)	0 (0%)
Quality of sleep	6 (2%)	24 (8%)	231 (75%)	42 (14%)	6 (2%)	1 (0%)
Amount of alcohol intake	30 (10%)	21 (7%)	245 (79%)	5 (2%)	1 (0%)	8 (3%)
Adherence to taking medications	6 (2%)	3 (1%)	284 (92%)	11 (4%)	2 (1%)	4 (1%)
The stress score for each answer	−2	−1	0	+1	+2	0

COVID-19, coronavirus disease 2019.

factors: office MAP from January to March 2020, worsening dietary intake, decreased frequency of eating lunch or dinner at home and decreased exercise volume, with coefficient values (95% confidence interval [CI]) of −0.42 (−0.51, −0.33), 2.66 (0.74–4.57), 2.08 (0.30–3.85) and 1.35 (0.09–2.61), respectively ($P < 0.001$, $P = 0.007$, $P = 0.02$ and $P = 0.04$, respectively). No significant correlations between ΔMAP, ΔBW and ΔHbA_{1c} were identified; the Pearson correlation coefficients were 0.04 for the relationship between ΔMAP and ΔHbA_{1c} ($P = 0.49$), −0.04 for the relationship between ΔBW and ΔMAP ($P = 0.49$), and 0.05 for the relationship between ΔBW and ΔHbA_{1c} ($P = 0.42$).

PS-matched cohort model

The PS-matched cohort model included 106 patients per group. The clinical characteristics of the unmatched and matched cohort models before the state of emergency announcement are shown in Table 4. There were significant differences in SBP, DBP, MAP, and history of cardiovascular disease between the $\Delta BP \leq 0$ and $\Delta BP > 0$ groups ($P < 0.001$, $P < 0.001$, $P < 0.001$ and $P = 0.02$, respectively). No significant differences between the groups were observed in the PS-matched model.

The absolute standardized difference of $<1.96 \times \sqrt{2/n}$ for the measured covariates showed the appropriate balance between the groups[25]. This borderline in the present matched cohort model ($n = 106$ per group) was 0.27 ($=1.96 \times \sqrt{2/106}$), and all standardized differences in the clinical characteristics of the patients were <0.27 in this matched cohort model. Histograms of the PSs before and after matching are shown in Figure S1.

The frequency with which each type of stress was reported as having worsened and the clinical findings after the state of emergency announcement are shown in Table 5. More patients reported that their dietary and salt intake had worsened in the $\Delta BP > 0$ group than in the $\Delta BP \leq 0$ group (9% vs 20%, $P = 0.02$, and 3% and 10%, $P = 0.04$, respectively). The total stress scores were determined based on responses to the stress-related questions in the questionnaire. These were higher in the $\Delta BP > 0$ group than in the $\Delta BP \leq 0$ group (0.05 ± 2.61 and 0.93 ± 2.70, respectively, $P = 0.03$).

DISCUSSION

Several retrospective studies reported that increased physical stress or inappropriate dietary intake caused by the COVID-19 pandemic induced the worsening of HbA_{1c} levels and BW in Japanese patients with diabetes mellitus[11–18]. Tanaka *et al.*[13] reported the different processes for the increase in BW and the reduced glycemic control depending on age under the state of emergency. With respect to prevention against the worsening of glycemic control, improving inappropriate dietary behavior[12] or seeking telemedicine or regular clinic visits during the state of emergency was suspected[26]. In contrast, significant worsening of glycemic control was not observed in patients with diabetes mellitus after the announcement of the COVID-19 pandemic[18,27,28]. Among these studies, Masuda *et al.*[18] reported that HbA_{1c} levels significantly decreased in the unstressed group, whereas Terakawa *et al.*[28] suggested a relationship between the worsening of glycemic control and living and working environments. Final conclusions for the change in HbA_{1c} during the COVID-19 pandemic could not be drawn from these retrospective studies, including the present study. Nevertheless, the most important thing that general practitioners should be aware of is that the worsening of physical activity, mental stress and inappropriate dietary intake can induce worsening of glycemic control and an increase in BW in patients with diabetes mellitus. Endo *et al.*[19] reported increases in BP after the announcement of the COVID-19 pandemic. BP control is also important in the management of diabetes mellitus, and its worsening can be one of the most serious concerns among patients with diabetes mellitus during the COVID-19 pandemic. Endo *et al.*[19] reported that the COVID-19 pandemic worsened the glycemic and BP control, even in patients who perceived no marked change in their diet or exercise. The present study showed a significant increase in office BP among patients with diabetes mellitus after the state of emergency announcement, without significant changes in HbA_{1c} or BW. Furthermore, the PS-matched model showed a significant relationship between worsening dietary and salt intake and an increase in BP after the state-of-emergency announcement. Additionally, patients with diabetes mellitus who experienced an increase in BP had higher total stress scores. Previous retrospective studies reported imbalanced characteristics of patients, and were unable to consider the effects of confounding factors. Although a randomized control study is the most reliable research method, it is practically impossible to carry one out during the COVID-19 pandemic. The present study is the only one that utilized a PS-matching method to balance the characteristics of the patients in each group, and we believe that the results of the analysis with reduced bias have great significance.

Natural disasters, such as earthquakes, typhoons or heavy rains, induce an increase in people's daily life stress. Kario *et al.*[1] reported that the BP profiles of three patients changed from white coat hypertension to sustained hypertension, and that there was an increase in cardiovascular events immediately after the Hanshin-Awaji earthquake[2]. Furthermore, the Great East Japan Earthquake was noted to influence early morning home-based BP management among patients who did not live near the epicenter of the earthquake[3]. Fath *et al.*[29] reported a transient increase in BP after just 1–2 weeks after the earthquake, and a return to original BP levels more than 1 month after the earthquake. Mechanical (e.g., cold, noise and radiation), biological (e.g., inflammation, infection and hunger), chemical (e.g., air pollution and drugs) and psychological (e.g., sadness, anger and anxiety) factors can induce stress. In relation to one another, these factors contribute to total stress after natural disasters. However, sometimes after such disasters, the stress becomes psychological stress[30]. Furthermore, our previous study showed a significant decrease in BP at home and a significant increase in office BP, which caused an increase in white coat hypertension among patients who regularly visited general practitioners[4]. Here, worsening dietary and salt intake, and higher total stress scores among patients with diabetes mellitus were more prevalent in the $\Delta BP \geq 0$ group than in the $\Delta BP < 0$ group, suggesting that increased stress influenced their dietary and salt intake. Elevated BP in the office was also noted. Thus, BW management and salt restrictions should be considered in stressful situations involving disasters.

In the present study, 145 patients with diabetes mellitus (47%) experienced increased stress in daily life after the state of emergency announcement in response to the rapid spread of COVID-19, and 156 (50%) responded that at least one daily activity worsened. To our knowledge, there is no evidence that patients with diabetes mellitus are more easily infected with COVID-19[8,9,10]; however, they are at an increased risk for

Table 4 | Clinical characteristics of patients in both groups before and after propensity score matching

	Unmatched cohort model			Matched cohort model		
	ΔBP ≤0 n = 146	ΔBP >0 n = 164	*P*-value	ΔBP ≤0 n = 106	ΔBP >0 n = 106	Standardized difference
Age	67.8 ± 10.4	69.3 ± 12.0	0.24†	68.8 ± 10.0	68.5 ± 12.1	0.03
Sex (male)	95 (65%)	102 (62%)	0.60‡	67 (63%)	67 (63%)	0.0
Hypertension	142 (97%)	158 (96%)	0.65‡	102 (96%)	103 (97%)	0.05
Dyslipidemia	140 (96%)	159 (97%)	0.61‡	102 (96%)	102 (96%)	0.0
Chronic kidney disease	86 (59%)	104 (63%)	0.42‡	61 (58%)	61 (58%)	0.0
Cardiovascular disease	26 (28%)	48 (29%)	0.02‡	22 (21%)	20 (19%)	0.05
SBP	144.8 ± 18.4	134.3 ± 18.2	<0.001†	139.9 ± 15.5	139.7 ± 17.1	0.01
DBP	81.5 ± 12.6	73.9 ± 11.1	<0.001†	77.7 ± 10.9	77.6 ± 9.9	0.01
MAP	102.6 ± 13.0	94.0 ± 11.3	<0.001†	98.4 ± 10.7	98.3 ± 9.6	0.01
BW	65.6 ± 12.5	64.4 ± 12.3	0.40†	64.2 ± 11.7	64.6 ± 12.9	0.03
eGFR	70.4 ± 20.6	67.6 ± 19.0	0.21†	68.8 ± 19.8	69.5 ± 19.7	0.04
HbA1c	50.8 ± 1.0 (6.8 ± 0.9)	51.3 ± 10.8 (6.8 ± 1.0)	0.68†	51.1 ± 9.6 (6.8 ± 0.9)	50.9 ± 10.4 (6.8 ± 1.0)	0.02
LnACR	2.48 ± 1.21	2.48 ± 1.41	0.99†	2.49 ± 1.24	2.47 ± 1.51	0.01
Salt intake	9.6 ± 2.0 (*n* = 122)	9.2 ± 2.0 (*n* = 147)	0.10†	9.5 ± 2.1 (*n* = 89)	9.1 ± 2.0 (*n* = 97)	
Antihypertensive agents						
ARB	82 (56%)	87 (53%)	0.58‡	58 (55%)	58 (55%)	0.0
ACEI	9 (6%)	16 (10%)	0.25‡	7 (7%)	7 (7%)	0.0
Ca channel blocker	70 (48%)	76 (46%)	0.78‡	51 (%)	47 (44%)	0.08
β-Blocker	22 (15%)	28 (17%)	0.63‡	16 (15%)	13 (12%)	0.08
Thiazide	6 (4%)	7 (4%)	0.95‡	5 (5%)	4 (4%)	0.05
Mineralocorticoid receptor blocker	11 (8%)	12 (7%)	0.94‡	5 (5%)	5 (5%)	0.0
Loop diuretic	2 (1%)	3 (22%)	0.75‡	1 (1%)	2 (2%)	0.08
Hypoglycemic agents						
DPP4 inhibitor	68 (47%)	69 (42%)	0.43‡	46 (44%)	47 (44%)	0.02
Metformin	41 (28%)	48 29 (%)	0.82‡	31 (29%)	30 (28%)	0.02
SGLT2 inhibitor	32 (22%)	31 (19%)	0.51‡	21 (20%)	20 (20%)	0.02
Insulin	22 (15%)	26 (16%)	0.85‡	17 (16%)	12 (11%)	0.14
Sulfonylurea	27 (19%)	32 (20%)	0.82‡	17 (16%)	19 (18%)	0.05
GLP-1 receptor agonist	9 (6%)	11 (7%)	0.85‡	8 (8%)	9 (9%)	0.03
Pioglitazone	16 (11%)	16 (10%)	0.73‡	11 (10%)	11 (10%)	0.0
α-Glucosidase inhibitor	28 (19%)	37 (23%)	0.47‡	21 (20%)	21 (20%)	0.0
Glinide	16 (11%)	14 (9%)	0.47‡	12 (11%)	10 (9%)	0.06
Statin	120 (83%)	135 (82%)	0.98	88 (83%)	83 (78%)	0.12
Ezetimibe	27 (19%)	33 (20%)	0.72‡	18 (17%)	19 (18%)	0.02
Antiplatelet	34 (23%)	43 (26%)	0.55‡	27 (26%)	24 (23%)	0.07

Data shown are shown as the mean ± standard deviation, or numbers (%). †Unpaired *t*-test. ‡χ^2-test. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BW, bodyweight; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA_{1c}, hemoglobin A_{1c}; LnACR, logarithmic value of urine albumin-to creatinine ratio; MAP, mean arterial pressure; SBP, systolic blood pressure; SGLT2, sodium–glucose cotransporter 2.

Table 5 | Ratios of the worsening of each stress and the clinical findings after a state of emergency

	ΔBP ≤0 (*n* = 106)	ΔBP >0 (*n* = 106)	*P*-value (McNemar's test)
Ratios of the worsening of each stress			
Daily stress	43 (41%)	53 (50%)	0.29†
Diet intake	9 (9%)	21 (20%)	0.02†
Salt intake	3 (3%)	11 (10%)	0.04†
Frequency of lunch or dinner at home	4 (4%)	2 (2%)	0.86†
Amount of exercise	31 (29%)	43(41%)	0.14†
Quality of sleep	17 (16%)	18(17%)	1.0†
Alcohol intake	1 (1%)	3(3%)	0.63†
Adherence to taking medications	3 (3%)	8(8%)	0.18†
Total stress score	0.05 ± 2.61	0.93 ± 2.7	0.03
Clinical findings after a state of emergency			
SBP	130.6 ± 14.3	150.1 ± 16.4	<0.001‡
DBP	72.2 ± 10.7	85.1 ± 10.6	<0.001‡
MAP	91.6 ± 10.2	106.8 ± 10.3	<0.001‡
BW	64.1 ± 11.7	64.6 ± 13.0	0.77‡
eGFR	67.6 ± 19.7	69.7 ± 19.2	0.44‡
HbA_{1c}	51.1 ± 9.4 (6.8 ± 0.0.9)	51.7 ± 10.1 (6.9 ± 0.9)	0.67‡
LnACR	2.42 ± 1.20	2.64 ± 1.43	0.23‡
Salt intake	9.2 ± 2.5	9.4 ± 2.5	0.67‡

Data shown are shown as the mean ± standard deviation, or numbers (%). †Paired *t*-test. ‡Wilcoxon signed-rank test. BW, bodyweight; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; LnACR, logarithmic value of urine albumin-to-creatinine ratio; MAP, mean arterial pressure; SBP, systolic blood pressure.

severe COVID-19[10,31]. Additionally, a higher mortality rate has been reported among patients with diabetes mellitus with poor glycemic control[32].

Several reports have shown a relationship between disasters and glycemic control among patients with diabetes mellitus in Japan. Inui *et al.*[33] reported that plasma glucose levels in patients with diabetes mellitus were elevated for a maximum of 3 months after the Hanshin-Awaji earthquake in Kobe City, which was the epicenter of the earthquake. However, no elevation in plasma glucose levels was noted in a neighboring city (Osaka City)[33]. In their study, the General Health Questionnaire scores, which were used to investigate the state of psychological distress or altered behavior related to the earthquake, were higher among patients with diabetes mellitus in Kobe City than in Osaka City[33]. Furthermore, high HbA_{1c} levels and General Health Questionnaire scores among patients with diabetes mellitus were related to the destruction of their houses or the death of close relatives[33].

Kirizuka *et al.*[34] identified that an inappropriate diet, discontinuation of medication, a decrease in exercise, the destruction of one's housing, long stays at a shelter, sex, age and pre-earthquake therapy were independent factors that correlated with the worsening of HbA_{1c} levels after the Hanshin-Awaji earthquake.

In the present study, an increase in BP, but not in HbA_{1c}, was noted among patients with diabetes mellitus after the state-of-emergency announcement. Among the 51 patients who responded "a little increase" or "much increase" for dietary intake, a significant increase in HbA_{1c}, SBP and BW was noted after the state of emergency announcement (from 50.1 ± 10.3 [6.7 ± 0.9] to 51.8 ± 10.5 [6.9 ± 1.0] mmol/mol (%), $P = 0.04$; from 135.3 ± 15.6 to 143.7 ± 16.1 mmHg, $P < 0.001$; and from 70.7 ± 13.5 to 70.7 ± 14.0, $P = 0.005$, respectively). In circumstances such as after a state of emergency announcement and after an earthquake, the subsequent dietary changes caused an increase in not only HbA_{1c} levels but also BP. Consequently, the importance of considering the dietary intake was reconfirmed, particularly in emergency situations.

The state of emergency announcement in Japan is a situation different from the lockdown in other countries; hence, the influence on the changes in BP might be different. Some reports on the changes in BP during the COVID-19 pandemic were published. In the USA, a significant increase in BP was observed during and after the COVID-19-related lockdown[35]. In contrast, a significant decrease in BP occurred after the COVID-19-related lockdown in France[36] and Italy[37], and no obvious change was observed in Brazil[38].

We suspected some reasons for the significant decrease in BP at home during the state of emergency. First, the season changed from winter to spring, and BP tended to be lower as the temperature increased. Second, the present study was an observational study with no restrictions on the change in treatment; general practitioners might have added antihypertensive medications to achieve the target BP. According to our previous report, the target BP achievement rate improved from 18%

(from April to June in 2019) to 31% during the state of emergency[4]; thus, the second reason seems more likely.

Wojciechowska *et al.*[39] reported that aircraft noise reduction during the lockdown was associated with a decrease in BP. This suggests that a reduction in daily social stress might lower BP, even during lockdown. Considering that the COVID-19 pandemic has a varied impact on people, understanding the various stresses among people is important to evaluate the changes in BP. In Japan, patients felt much stress outside and always wore masks for fear of acquiring the COVID-19 infection. Such stress had an immediate influence on the sympathetic system, and the office BP increased during the state of emergency. With respect to ΔHbA_{1c}, the short observation periods might be related. As for ΔBW, multiple linear regression analysis showed that worsening dietary intake was an independent factor for ΔBW, with coefficient values of 0.23 (95% CI 0.09–0.97; $P = 0.02$). After the state of emergency, BW was greater in the ΔBP >0 group than in the ΔBP ≤0 group (64.6 ± 13.0 vs 64.1 ± 11.7, respectively), and a significant difference might be observed in a large-scale survey.

Elevated HbA_{1c} levels were noted not only in patients with type 2 diabetes mellitus, but also in those with type 1 diabetes mellitus. Kamio *et al.*[40] reported that elevated HbA_{1c} levels were present for 3–12 months after the 2004 Mid-Niigata Prefecture earthquake. A significant relationship between elevated HbA_{1c} levels and low serum C-peptide levels was observed at 3 months after the Great East Japan Earthquake in 2011[41]. In addition, Kamimura *et al.*[42] reported that HbA_{1c} levels were elevated at 1–2 months after the Great East Japan Earthquake in 2011, and that elevated HbA_{1c} levels were related to psychological stress not only in shelters, but also in patients' own homes. An increase in cortisol or catecholamine secretion[43], sleep disruption and circadian misalignment[44] were thought to be the mechanisms underlying the worsening of glycemic control after disasters, which caused stress or anxiety among patients. Interestingly, glycemic control in patients with type 2 diabetes mellitus unexpectedly worsened at 1–2 months after the Kumamoto earthquake in 2016, and this decrease was negatively correlated with the prompt recovery of lifelines and a sufficient amount of sleep, which might contribute to emotional stability[45].

Sisman *et al.*[46] reported that worsening glycemic control and an increase in dietary intake, especially carbohydrate consumption, during the COVID-19 pandemic were related to higher anxiety and depression scores. Stress led to not only elevated BP, but also poor glycemic control[47,48], and was related to various comorbidities[49]. We compared the clinical data before and after the state of emergency announcement. The observation period of several months in the present study might not have been sufficient to detect worsening glycemic control resulting from an increase in dietary intake. Thus, a longer observational study is necessary to determine the long-term influence of the COVID-19 pandemic on patients with diabetes mellitus.

In the present retrospective observational study, data on clinical measurements were only collected at one point during the state of emergency. If the period of the state of emergency or COVID-19 pandemic is prolonged, daily stress (including inappropriate dietary or salt intake) might further increase, which could induce the worsening of glycemic and BP control in patients with diabetes mellitus. Naturally, such worsening of clinical control will result in the progression of diabetes mellitus complications, and the increase in ACR should be monitored. Owing to the ongoing COVID-19 pandemic of >2 years, future long-term observational studies are required to evaluate the ongoing influence on stress and BP. Furthermore, applying the results of the present study to the general public is difficult, because the patients analyzed in this study were limited to those with type 2 diabetes mellitus.

The PS-matching method is useful for reducing bias that might influence the results of the present retrospective observational study. However, the clinical parameters and patient data were limited, and the covariates that we could not review or adjust for might have introduced bias. Furthermore, among 310 patients, the data of just 212 were analyzed using the PS-matching method, and the findings of this study do not necessarily apply to patients excluded from the study. PS stratification or inverse probability weighting might make the results generalizable, as these methods use the whole patient sample. Further large-scale surveys, prospective surveys or meta-analyses are required to draw the final conclusion.

In conclusion, an increase in stress and, particularly, worsening dietary and salt intake were noted among patients with type 2 diabetes mellitus who experienced an increase in BP after the state-of-emergency announcement related to the COVID-19 pandemic. A strategy for preventing worsening dietary intake in stressful situations, such as during a state of emergency, is necessary.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

ETHICAL APPROVAL

The present study was approved by the special ethics committee of the Kanagawa Medical Association, Japan (Japan Physicians Association of Internal Medicine 028-2008-001, 4 December 2020), and carried out according to the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare of Japan.

DATA AVAILABILITY STATEMENT

Data are available from the Sagamihara Physicians Association. Data access for investigators is bound by confidentiality agreements.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | The histogram of the distribution of propensity score before and after matching.