Short-term Effects of Prosthetic Mandibular Advancement on Glycemic Control in Diabetic Patients with Obstructive Sleep Apnea Syndrome

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Running title: Effects of PMA on DM Patients with OSAS

Abstract

The association between obstructive sleep apnea syndrome (OSAS) and glucose intolerance has been reported in previous study. However, the effects of prosthetic mandibular advancement (PMA) on blood glucose levels and insulin resistance remain unclear. The objective of this study was to investigate the short-term effects of PMA on glycemic control in type 2 diabetes mellitus (T2DM) patients with OSAS. Thirty-four T2DM patients were diagnosed with OSAS based on a two-channel (airflow and SpO_2) portable sleep apnea monitor. These patients were divided into two groups: 18 patients who underwent PMA (Group 1) and 16 patients who were unable to undergo PMA (Group 2). In Group 1, a significant difference was observed in the respiratory disturbance index obtained before and after using the PMA (baseline, 17.7 ± 9.8; with PMA, 8.3 ± 7.7, $p<0.001$). The usage of the PMA caused significant improvements of the changes in fasting blood sugar levels after two days and HbA1c levels from those of the baseline levels after one month and three months from those of the baseline levels (baseline, 8.3±1.4%; after one month, 7.6±1.2%; after three months, 7.3±1.1%,respectively, $p<0.05$). Our results suggest that PMA may have an effect on glycemic control in T2DM patients with OSAS.

[200 words]

Keywords : Obstructive sleep apnea, Prosthetic mandibular advancement, Type 2 diabetes mellitus, Glucose intolerance, Apnea-hypopnea index

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Introduction

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive cessation of breathing during sleep with daytime consequences, including subjective daytime sleepiness, and impaired cognitive function and memory. Approximately 3%–19% adult males and 1.2%–15% adult females in the general population suffer from OSA defined by an apnea–hypopnea index (AHI) of ≥5 and daytime hypersomnolence [1-4].

The association between OSA and glucose intolerance has been reported previously [5-8], and a previous study estimated that the prevalence of OSA in patients with type 2 diabetes mellitus (T2DM) was 86.3% [9]. Previous reports have also shown a relationship between OSA and obesity. Moreover, OSA is reported to be independently associated with metabolic syndrome, hypertension, insulin resistance, impaired glucose tolerance, and dyslipidemia [5,10,11]. Therefore, it is essential to recommend OSA patients to receive suitable therapies to treat the abovementioned conditions when present. Nasal continuous positive airway pressure (CPAP) therapy has been globally accepted as the first-line therapy for T2DM with OSA [5,12-14]. However, Grimaldi et al. emphasized the necessity to prolong the CPAP duration to at least 6 to 7 h per night in order to cover maximum rapid eye movement (REM) sleep [15]. Although prosthetic mandibular advancement (PMA) therapy is less effective than CPAP, it may alleviate disordered breathing during REM sleep if used throughout the night.

During the last two decades, PMA therapy has also been shown to be effective against OSA [16]. PMA therapy causes the mandible to protrude forward, thus preventing or minimizing upper airway collapse during sleep.

It prevents sleep apnea, which induces hypoxia [17-19]. The largest randomized controlled trial of CPAP vs. PMA therapies showed that CPAP therapy was more efficacious than PMA therapy in decreasing AHI, although the compliance rate was higher with PMA therapy [20]. Therefore, the comfort of patients with OSA who consent to undergo treatment should not be neglected [16].

Although the effects of OSA treatment with CPAP on glycemic control have been mostly reported [5,12-14], those of OSA treatment with PMA have not. The aim of this study was to evaluate the short-term effects of PMA therapy on glycemic control in T2DM patients with OSA by measuring and comparing fasting blood sugar (FBS) and hemoglobin A1c (HbA1c) levels before and after PMA therapy.

Materials and Methods

Participants

Between August 2010 and April 2013, we evaluated 483 inpatients undergoing treatment for T2DM who attended a diabetes mellitus education program in the Department of Endocrinology and Diabetes Mellitus, Fukuoka University Hospital, Japan. Of the total, 74 inpatients who gave their consent to participate in the study underwent assessment of the degree of sleep apnea using a two-channel (airflow caught by only a nasal pressure transducer and SpO_2) portable sleep apnea monitor (LS-120/120S, Fukuda Denshi Co., Ltd., Tokyo, Japan) in the hospital ward. Patients with cerebrovascular, neurological, or chronic respiratory diseases were excluded. Of the 74 patients, 28 patients had AHI < 5 according to an

overnight apnea monitoring experiment. The remaining 46 patients had AHI ≥ 5 and were diagnosed with OSA. Of these 46 patients, 12 discontinued PMA therapy within 3 months because of stomatitis (n = 4), lack of improvement (n =1), and unclear reasons (n = 7). Eventually, 34 inpatients (19 males and 15 females; mean age, 64.8 ± 9.7 years) with T2DM were enrolled in this study (Table 1). The study was approved by the ethics committee of the Fukuoka University Hospital, and informed consent was obtained from all patients. Obstructive apnea was defined as the absence of or a minimum least 90% decrease in nasal airflow for at least 10 s accompanied by continued or increased in respiratory effort. Hypopnea was defined as a minimum 30% decrease in nasal airflow for at least 10 s accompanied by a minimum 4% decrease in oxygen saturation. AHI was calculated as the total number of apneas and hypopnea events divided by the total recording time in hours.

The participants were divided into two groups: Group 1, including 18 patients who underwent PMA therapy (5 ≤ AHI < 15) and/or were unable to accept CPAP therapy despite a moderate AHI of ≥ 15, and Group 2, including 16 patients who did not undergo PMA therapy (5 ≤ AHI < 30; Fig. 1). The reasons why the Group 2 patients could not undergo PMA therapy included refusal to wear the devise in 9 patients, requirement of dental treatment before PMA therapy in 7, and the presence of moderate or severe OSA (AHI of ≥15) requiring CPAP therapy in 2. All patients were hospitalized for T2DM treatment and were attending a diabetes mellitus education program; therefore, the 9 patients who refused to wear the PMA devise may not have felt the need for OSA treatment. These patients did not

receive any other OSA treatment.

Type of PMA and titration

All PMA devices were fabricated by the same dentist. The device used in this study was fabricated using heat-cured acrylic polymer.

To wear a PMA device, patients are required to have at least 10 maxillary and 10 mandibular teeth. The patients in Group 1 had a sufficient number of teeth to help in retention of the PMA device, with the ability to protrude the mandible forward by ≥6 mm, i.e., up to 70% of the maximum mandibular advancement. They wore the PMA device for approximately 1 week after hospitalization when they completed the first stage of the diabetes mellitus education program. Their antiglycemic therapy remained constant during the study period. The amount of mandibular advancement was adjusted by evaluating changes in the upper and lower pharyngeal airway spaces during mandibular advancement using cephalometry and fiberoptic endoscopy.

Examination and assessment

In Group 1, AHI was measured before and 2 days after PMA therapy. FBS, blood pressure, and low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were measured before, 2 days after, and 1 and 3 months after PMA therapy. In addition, HbA1c levels were measured before and after 1 and 3 months after PMA therapy. In Group 2, the same clinical parameters were evaluated on the day of hospitalization and 1 and 3 months after hospitalization.

Statistical analysis

Differences in patient characteristics and sleep apnea monitor findings which exhibited a normal distribution, were compared between the two groups using the unpaired *t*-test, and the chi-squared test, while the other datasets compared using the Mann-Whitney *U* test. Differences in sleep apnea monitor findings before and after PMA therapy were compared using the paired *t*-test. Two-way repeated measures ANOVA with post-hoc tests was used to compare FBS and HbA1c levels at baseline with those at 2 days (only FBS levels), 1 month, and 3 months after PMA therapy. A *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS statistical software package (version 12.0J; SPSS Inc., Chicago, IL, USA).

Results

There was no significant difference in the characteristics of patients at baseline and in the apnea monitor findings between the two groups (Table 1, 2). Uninterpretable data, such as those obtained when the participants woke up to use the washroom or other activities, in the sleep studies was excluded from analysis (Group 1, 87.5 ± 31.4 min; Group 2, 94.1 ± 32.3 min).

No participants in Group 1 complained of jaw discomfort. From the patients' medical records, no differences were observed in food and caloric intake between before and after PMA therapy. The patients wore the PMA device during bed time (at least ≥5 h) for 3 months. In Group 1, a significant difference was observed between AHI at baseline and that after PMA therapy (baseline, 17.7 ± 9.8; after PMA, 8.3 ± 7.7, $p < 0.001$; Table

3). There was a significant increase in the minimum oxyhemoglobin saturation from 79.8 ± 6.0% to 85.7 ± 4.5% after using the PMA ($p < 0.001$) and the mean oxyhemoglobin saturation from 94.6 ± 1.8% to 95.9 ± 1.8% ($p = 0.03$) after PMA therapy. With regard to apnea, hypopnea, and 4% oxygen desaturation episodes, significant differences were observed between values at baseline and those after PMA thrapy.

A significant decrease was observed between FBS levels at baseline and those at 2 days after PMA therapy (152.1 ± 39.9 mg/dL vs. 133.6 ± 30.7 mg/dL; $p = 0.015$: Fig.1). HbA1c levels were also significantly different at baseline and at 1 and 3 months after PMA therapy (baseline, 8.3 ± 1.4%; at 1 month, 7.6 ± 1.2%; and at 3 months; 7.3 ± 1.1%, respectively, with $p = 0.01$ and after three months; $p = 0.012$, respectively; Fig.2). Although no significant differences were observed between the two groups (FBS, $p = 0.145$; HbA1c, $p = 0.708$), Group1 showed a greater improvement in FBS and HbA1c levels compared with Group2. There was no significant difference between blood pressure, LDL-C levels, HDL-C levels, and TG levels at baseline and those at 1 month after PMA therapy.

Each group showed a significant differences between the body mass index (BMI) on the day of hospitalization and at 3 months after hospitalization (Group 1, 27.1 ± 5.3 vs. 25.7 ± 4.6, $p=0.007$; Group 2, 25.8 ± 3.7 vs. 24.9 ± 3.2, $p=0.002$). However, there was no significant difference in the rate of change in BMI between the two groups ($p = 0.35$).

Discussion

OSA is characterized by repetitive episodes of upper airway obstruction

occurring during sleep, generally in association with a decrease in blood oxygen saturation [19]. Previous studies have shown that OSA is associated with insulin resistance and T2DM [5,6,10,22-26]. In this study, we assessed the short-term effects of PMA therapy on glycemic control in T2DM patients with OSA.

To the best of our knowledge, this study is the first to evaluate the impact of PMA therapy on glycemic control in patients with OSA. Improvement of intermittent hypoxemia by the use of a PMA device during sleep indicated a beneficial effect on glycemic control in this study. It appears that any significant improvement in AHI and oxygen saturation levels associated with PMA therapy may have an immediate effect on blood glucose levels in T2DM patients. In this study, FBS levels decreased in only 2 days, while HbA1c levels also decreased in a month's time. These short-term changes decreased the influence of possible confounding factors such as insulin and diet therapy and suggested the immediate effects of PMA therapy on not only OSA but also glycemic control. With regard to change in FBS levels, the absence of a significant improvement at 1 month after PMA therapy may have been caused by changes in the patient's diet during and after hospitalization. Although it is important to maintain compliance with T2DM treatment, a convenient therapeutic option such as PMA therapy is meaningful for T2DM patients with OSA.

Previous studies showed that the association of insulin resistance with age, BMI, and the 4% oxygen desaturation index and concluded that the most reliable predictor of insulin resistance was the 4% oxygen desaturation index, not BMI [23]. Furthermore, it has been reported that the severity of

OSA is associated with the degree of insulin resistance, and that intermittent hypoxemia caused by recurrent apnea and hypopnea is likely to be an important intermediate factor in the causal pathway [12].

Tamura et al. listed some intermediate factors in the causal pathway between OSA and impaired glucose metabolism, including the activation of the sympathetic nervous system, sleep loss and sleep deprivation, recurrent intermittent hypoxemia, and obesity [22]. Many studies have investigated and mentioned recurrent intermittent hypoxemia as one of the intermediate factors [27-33]. One of these studies concluded that the most reliable predictor of insulin resistance was the 4% oxygen desaturation index, not BMI [6]. Sulit et al. reported that the strongest index associated with impaired glucose tolerance was the time spent at an oxygen saturation of <90% [34]. In our study, the 4% oxygen desaturation index decreased from14.0 ± 8.6 at baseline to 8.6 ± 7.8 after PMA therapy (p = 0.002; Table 3). The decreases in FBS and HbA1c levels in our patients may have been caused by an improvement in intermittent hypoxemia. To evaluate insulin resistance, we measured serum C-peptide levels instead of HOMA-IR in five patients in this study because the latter may be influenced by insulin therapy. In four of the five patients, the serum C-peptide level decreased 2 days after PMA therapy compared with that at baseline (baseline, 3.3 ± 1.1%; after 2 days, 2.5 ± 1.6%; after three months, 2.4 ± 0.8%). Although there is a need for further data, these findings suggest a possibility that PMA therapy improves insulin resistance in T2DM patients with OSA. Unfortunately, our results did not provide any information about sleep loss and sleep deprivation because we did not analyze sleep problems using a complete

polysomnography examination. There was no significant difference in the improvement of FBS and HbA1c levels between the obese and nonobese patients. This finding may support the hypothesis that oxygen desaturation is a more reliable predictor of insulin resistance compared with BMI.

On the other hand, evidence on the effects of CPAP therapy on insulin resistance has been inconsistent [25]. Previous studies reported that CPAP therapy did not significantly change HbA1c levels in patients with impaired glucose tolerance or T2DM [23]. Babu et al. studied changes in interstitial glucose levels and measured HbA1c levels in 25 T2DM patients before and after CPAP therapy for OSA [12]. After CPAP therapy, they found a significant decrease in both 1-h postprandial glucose levels (baseline, 148 ± 200 mg/dL; after CPAP therapy, 83 ± 117 mg/dL, $p = 0.003$) and HbA1c levels (baseline, 9.2 ± 2.0%; after CPAP therapy, 8.6 ± 1.8%; $p = 0.02$). Furthermore, they showed a significant correlation between the decrease in HbA1c levels and the duration of CPAP therapy, indicating the importance of device compliance for metabolic improvements after CPAP therapy.

PMA therapy prevents upper airway collapse in patients with OSA. A recent guideline by the American Academy of Sleep Medicine concluded that oral appliances are less effective than CPAP therapy, although they are a reasonable alternative for select patients with mild to moderate OSA [35].

Both our study, which involved PMA therapy, and the study by Babu et al. [12], which involved CPAP therapy, showed a decrease in FBS (12% and 44%, respectively) and HbA1c levels (7% and 12%, respectively) indicating that the effects of PMA therapy on glycemic control are comparable to those of

CPAP therapy in OSA patients with T2DM. Although Babu et al. emphasized the importance of compliance with CPAP therapy [12], most OSA patients also exhibit good compliance with PMA therapy because they use the PMA device while sleeping [12]. Grimaldi et al. suggested that 4 h of CPAP use left 60% of REM sleep untreated, leading to insufficient improvements in HbA1c levels [15]. PMA therapy may be used for a longer duration than CPAP during sleep, thus covering more of the REM sleep cycle and resulting in better glycemic control.

The duration of T2DM in our patients was over 10 years (Group 1, 12.8 ± 12.3 years; Group 2, 11.0 ± 10.0 years; Table 1); however, the duration of OSA influence on their blood glucose levels and insulin resistance remains unclear. Considering the mean age of our patients (Group 1, 64.7 ± 10.8 years; Group 2, 64.9 ± 8.6 years; Table 1) and the mean AHI (Group 1, 17.7 ± 9.8 /h; Group 2, 16.9 ± 13.0 /h; Table 2), most participants may have developed the initial symptoms of OSA at least midway during the course of T2DM. T2DM in our patients was considered to be complicated by OSA for certain periods of time.

This study has some limitations. First, although the results of clinical examination are influenced by factors other than PMA therapy, such as insulin and diet therapy for T2DM or patient adherence to treatment, we only assessed the short-term effects of PMA therapy during hospitalization and at 1 and 3 months after PMA therapy. Despite this, FBS levels at 2 days and HbA1c levels at 3 months (which reflects mean glycemia levels for the previous 3 months) after PMA therapy were considered to be influenced mainly by PMA therapy. To evaluate the long-term effects of PMA therapy

on glycemic control, further adjustment of confounding factors is needed. Second, because we used a two-channel (airflow and SpO_2) portable sleep apnea monitor to assess the effects of PMA therapy, the mechanism by which PMA therapy affected sleep disorders remains unclear. We excluded patients with cerebral vascular or neuromuscular disorders from the study, not patients with central apneas perfectly. A complete polysomnography examination is required to explain the relationship between improvements in glycemic control and sleep problems.

Conclusion

Although there was no significant difference between patients who did and did not undergo PMA therapy in this study, the former showed a significant improvement in FBS and HbA1c levels after PMA therapy. Although the requirement for further controlled trials with a larger sample size and complete polysomnography examinations are required, the results of this study suggest that PMA therapy may improve glycemic control in T2DM patients with OSA.

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Figure legends

Fig. 1, Change of fasting blood sugar (FBS)

There was a significant difference in only Group 1 between baseline and after two days using the PMA.

Fig. 2, Change of hemoglobin A1c (HbA1c) (NGSP)

There were significant differences in only Group 1 between baseline and after one month, between baseline and after three months using the PMA.

Table 1. Patient characteristics at baseline

		Group 1 (n=18)	**Group 2** (n=16)	***p***
Age (year)		64.7±10.8	64.9±8.6	0.95
Male sex		50.0%	37.5%	0.35
Body mass index (kg/m^2)		27.1±5.3	25.8±3.7	0.42
Waist circumference (cm)		100.7±14.9	105.0±14.5	0.60
Epworth Sleepiness Scale score		5.9±3.6	5.1±3.8	0.55
Brinkman index		624.4±854.5	548.8±653.9	0.78
Alcohol (U/week)		7.6±10.8	14.3±21.6	0.26
Medications for diabetes mellitus	・Insulin+OHA	27.7%	50.0%	0.46
	・Insulin (U)	33.3% (10.8±11.9)	18.8% (11.9±14.8)	
	・OHA	22.2%	25.0%	
	・Dietetic treatment only	17.7%	6.2%	
Duration of Medications for diabetes mellitus (year)		12.8±12.3	11.0±10.0	0.65
Hypertension		66.7%	62.5%	0.54
Hyperlipidemia		50.0%	50.0%	1.0
Blood pressure (mmHg)	・systolic	128.0±23.1	134.4±17.6	0.37
	・diastolic	70.1±12.3	77.3±9.0	0.07
Fasting blood sugar (mg/dL)		152.1±39.9	152.4±34.0	0.98
HbA1c (NGSP)%		8.3±1.4	8.0±1.4	0.58
Low-density lipoprotein (mg/dL)		111.8±34.3	107.4±33.6	0.71
High-density lipoprotein (mg/dL)		49.7±11.7	44.3±16.8	0.28
Triglyceride (mg/dL)		161.5±130.4	198.9±164.6	0.48

※OHA: Oral hypoglycemic agent

Table 2. Comparison of the two groups of two-channel (airflow and SpO2) portable monitor findings at baseline between patients who did (Group 1) and did not undergo (Group 2) prosthetic mandibular advancement therapy

	Group 1 (n=18)	**Group 2** (n=16)	*p*
Total scoring time (min)	407.7±34.3	409.5±35.5	0.88
Respiratory disturbance index (/h)	17.7±9.8	16.9±13.0	0.82
Apnea episode (times/night)	86.3±70.8	80.3±81.5	0.82
Hypopnea episode (times/night)	35.3±27.9	37.6±30.7	0.82
4% oxygen desaturation episode (times/night)	95.6±60.2	105.8±79.7	0.67
4% oxygen desaturation index (/h)	14.0±8.6	15.3±10.8	0.71
Minimum SpO_2 (%)	79.8±6.0	81.4±10.6	0.58
Mean SpO_2 (%)	94.6±1.8	95.8±1.7	0.053

Table 3. Changes in two-channel (airflow and SpO2) portable monitor findings after prosthetic mandibular advancement therapy (Group 1; n = 18)

	Baseline	**With PMA**	*p*
Total scoring time (min)	407.7±34.3	383.8±61.8	0.15
Respiratory disturbance index (/h)	17.7±9.8	8.3±7.7	<0.001
Apnea episode (times/night)	86.3±70.8	40.3±49.4	<0.001
Hypopnea Episode (times/night)	35.3±27.9	15.7±10.2	<0.001
4% oxygen desaturation episode	95.6±60.2	53.7±48.5	<0.001
4% oxygen desaturation index (/h)	14.0±8.6	8.6±7.8	0.002
Minimum SpO_2 (%)	79.8±6.0	85.7±4.5	<0.001
Mean SpO_2 (%)	94.6±1.8	95.9±1.8	0.03

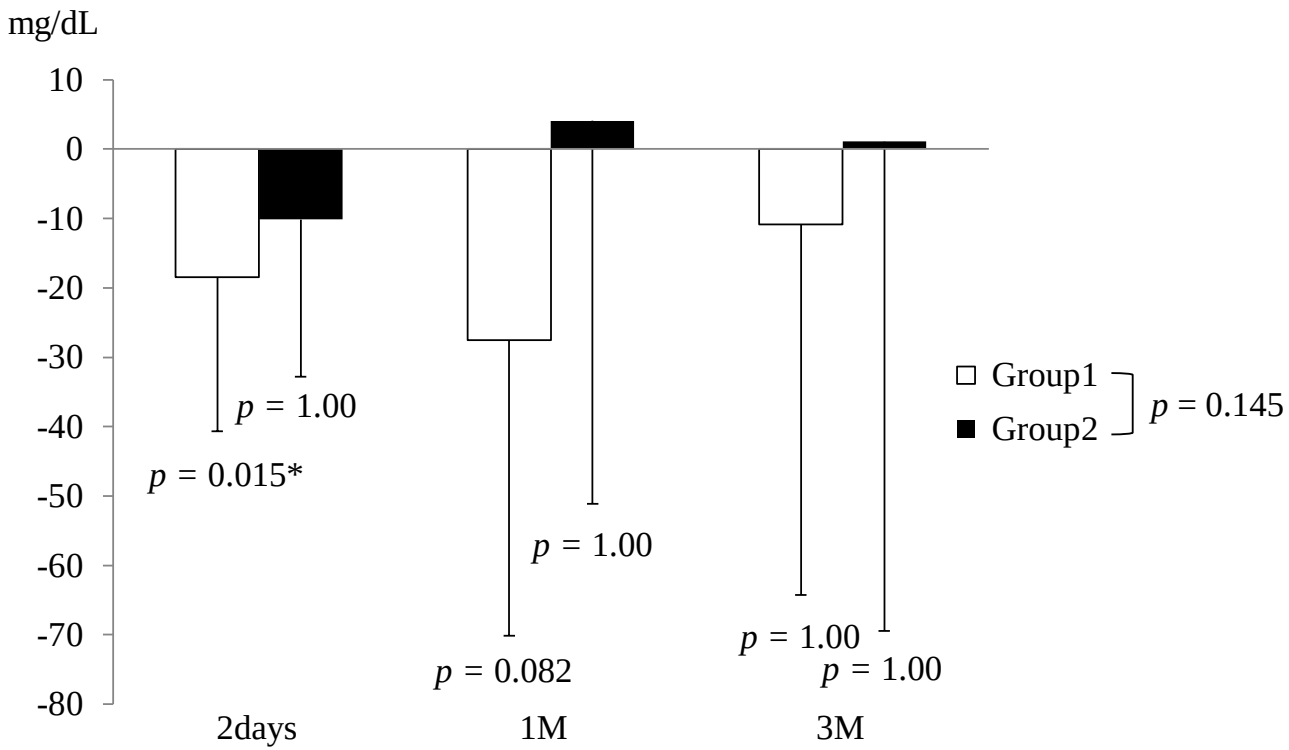

Fig.1 Change of fasting blood sugar (FBS)

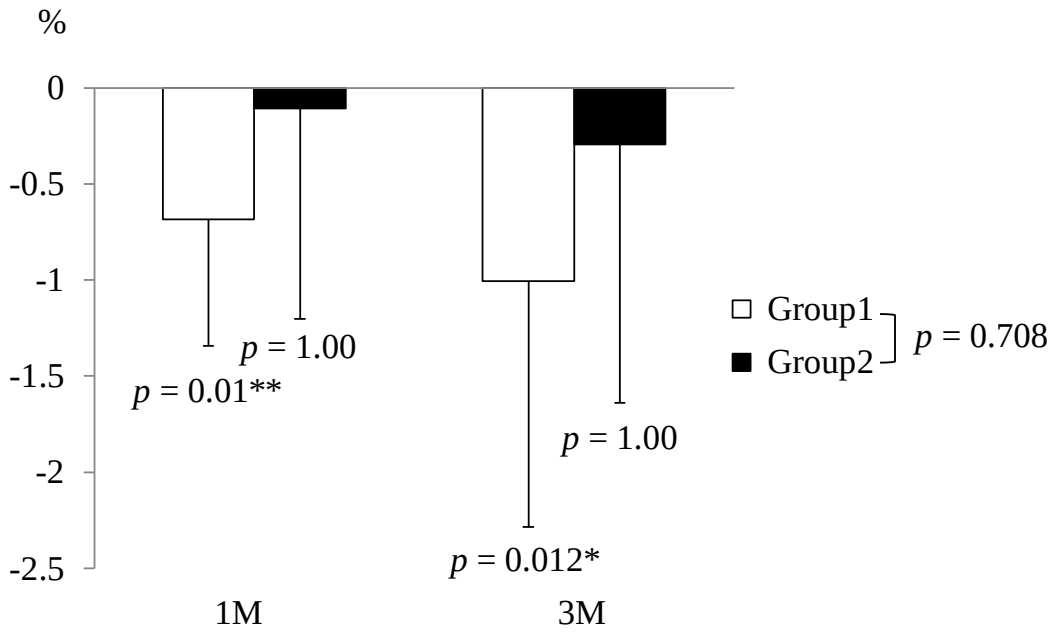

Fig. 2 Change of hemoglobin A1c (HbA1c) (NGSP)