

Article

Nocturnal Hypoglycemia in Individuals with Type 2 Diabetes Receiving Concomitant Use of DPP-4 Inhibitors and Sulfonylureas: An Analysis Using Continuous Glucose Monitoring

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Abstract

Background: Hypoglycemia has harmful effects on chronic complications of diabetes, and when it occurs at night, it is often asymptomatic. When oral hypoglycemic medications with different mechanisms of action that promote insulin secretion are used in combination in the individual with type 2 diabetes, hypoglycemia may occasionally occur. Therefore, we investigated blood glucose fluctuations with a focus on nocturnal hypoglycemia in the individuals with type 2 diabetes undergoing concomitant use of these medicines using continuous glucose monitoring (CGM) as a retrospective observational study. **Methods:** The participants consisted of 59 Japanese individuals with type 2 diabetes treated with a DPP-4 inhibitor and glimepiride (N = 30) or gliclazide (N = 29). Clinical factors including HbA1c were not significantly different between these groups. Blood glucose was monitored using CGM for 10 days. Hypoglycemia was defined as monitoring glucose less than 54 mg/dL for at least 15 min. **Results:** Asymptomatic nocturnal [from midnight to 6:00 AM (6 h)] hypoglycemia was observed more frequently in the glimepiride group (43.3%) than the gliclazide group (6.9%), $p = 0.002$. All hypoglycemia was unrecognized. Logistic regression analyses indicated that nocturnal hypoglycemia was significantly associated with concomitant use of a DPP-4 inhibitor and glimepiride. **Conclusions:** Among individuals with type 2 diabetes who had relatively good glycemic control, asymptomatic nocturnal hypoglycemia occurred more frequently in the group treated with a DPP-4 inhibitor and glimepiride than that treated with a DPP-4 inhibitor and gliclazide. Even when HbA1c levels were comparable, the use of CGM that could monitor nocturnal glucose fluctuation clearly identified this difference.



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Keywords: nocturnal hypoglycemia; unrecognized hypoglycemia; continuous glucose monitoring; DPP-4 inhibitor; sulfonylurea

1. Introduction

Recent reports [1,2] indicate that dipeptidyl peptidase-4 (DPP-4) inhibitors are the most commonly prescribed initial medications for individuals with type 2 diabetes in Japan. This is likely because DPP-4 inhibitors have a relatively low risk of causing hypoglycemia when used alone, even in individuals with impaired renal function. On the other hand, since the hypoglycemic effect of these drugs alone is not particularly strong [1,2], they

are sometimes used in combination with sulfonylurea (SU) drugs in clinical practice to achieve better glycemic control. However, it has also been reported [3] that inappropriate combinations (type or dose) of DPP-4 inhibitors and SU drugs can cause hypoglycemia by enhancing insulin secretion induced by these drugs.

We previously reported findings [4] from a study of individuals who visited our emergency department because of severe hypoglycemia caused by diabetes medications over a 10-year period from 2009 to 2018. While hypoglycemia due to SU drugs clearly decreased, the proportion of individuals receiving combination therapy with SU drugs (particularly glimepiride) and DPP-4 inhibitors increased. Numerous reports [5–9] indicate that hypoglycemia in individuals with diabetes adversely affects chronic complications. Among these, nocturnal hypoglycemia can induce severe arrhythmias and may sometimes be life-threatening [6]. This nocturnal hypoglycemia is often asymptomatic and difficult to detect.

On the other hand, the clinical application of continuous glucose monitoring (CGM) has made it possible to easily observe blood glucose fluctuations throughout the day. Numerous studies [10–14] have reported the clinical utility of CGM in individuals with type 1 and type 2 diabetes receiving insulin therapy. However, few reports exist concerning individuals with type 2 diabetes not receiving insulin therapy. Furthermore, the consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes in 2009 [15] recommended the use of SU drugs other than the long-acting glibenclamide. Consequently, the SU drugs used at our facility in recent years have been predominantly glimepiride or gliclazide. Therefore, we investigated glucose fluctuations, focusing on nocturnal hypoglycemia, using CGM in individuals with type 2 diabetes receiving combination therapy with DPP-4 inhibitors and the SU drugs (gliclazide or glimepiride).

2. Materials and Methods

The subjects were retrospectively selected from individuals who received CGM using FreeStyle LibrePro (Abbott Diabetes Care, Alameda, CA, USA) at our outpatient clinic between 2019 and 2020, meeting the following criteria: Specifically, participants were individuals with type 2 diabetes receiving combination therapy with a DPP-4 inhibitor and SU agent [glimepiride: ≤ 2 mg/day (Group A) or gliclazide: ≤ 80 mg/day (Group G)] for at least one year, achieving relatively good glycemic control (HbA1c: 6.0–7.9%). The maximum dose of these medications was determined based on recommendations [3] and our previous reports [16]. They had an estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m², and had no history of hypoglycemic symptoms. A total of 59 individuals met these criteria. Among these subjects, the only other diabetes medication used besides DPP-4 inhibitors and SU drugs was metformin (500 mg to 1000 mg/day: 21 subjects in Group A, 23 subjects in Group G). No other diabetes medications were administered. Regarding glimepiride, the dose was 1.3 (1.0:2.0) [1.4 ± 0.6] mg/day. Specifically, 7 participants received 0.5 mg/day, 8 received 1.0 mg/day, 2 received 1.5 mg/day, and 13 received 2.0 mg/day. Among these, one participant receiving 2.0 mg/day and three receiving 1.0 mg/day took the medication twice daily (after breakfast and after dinner), while the remaining 26 participants took it once daily (after breakfast). Gliclazide was administered at 20 (40:80) [52.4 ± 26.4] mg/day, with 8 participants receiving 20 mg/day, 8 receiving 40 mg/day, and 13 receiving 80 mg/day. All participants took these doses twice daily (after breakfast and after dinner). DPP-4 inhibitors used were sitagliptin (50 mg once daily after breakfast) or vildagliptin (50 mg twice daily after breakfast and dinner). All participants went to bed between 10:00 PM and 11:40 PM and woke up between 6:00 AM and 7:20 AM. The clinical data for these subjects are shown in Table 1. No significant differences were observed between

the two groups in terms of sex, age, body mass index (BMI), years after diagnosis, HbA1c, fasting serum C-peptide, eGFR, type of DPP-4 inhibitor, or frequency of concomitant metformin use. At our hospital's diabetes clinic, many patients visit every three months. During these visits, they receive not only a medical examination by a doctor but also dietary guidance from a registered dietitian and advice on daily living from a specialized nurse. All of the participants included in this study had received this guidance. They were also asked to use a log sheet titled "Daily Record" provided by Abbott Japan Co., Ltd. (Chiba, Japan) to note their daily meals, exercise, medication schedule, bedtime, and wake-up time, as well as any unusual occurrences, such as symptoms of hypoglycemia.

Table 1. Clinical data of the participants in study.

Group	A	G	<i>p</i>
N	30	29	
Gender (% of male)	53.3	48.3	0.797
Age (years old)	71.0 (66.3:73.8)	70.0 (66.0:74.0)	0.616
Body mass index (kg/m ²)	23.3 (21.9:26.2)	24.1 (23.3:25.8)	0.197
Years after diagnosis (years)	15.0 (11.3:20.5)	16.0 (11.0:20.0)	0.927
HbA1c (%)	7.2 (6.8:7.4)	7.1 (6.9:7.4)	0.994
Fasting serum C-peptide (ng/mL)	1.63 (1.08:2.16)	1.86(1.16:2.48)	0.274
eGFR (ml/min/1.73 m ²)	68.5 (61.5:77.3)	71.0 (58.0:78.0)	0.964
Combined usage of metformin (%)	83.3	79.3	1.000
Dose of sulfonylureas			
Glimepiride (mg/day)	1.25 (1.00:2.00) [1.4 ± 0.6]		
Gliclazide (mg/day)		40.0 (20.0:80.0) [52.4 ± 26.4]	
Number of individuals treated with DPP-4 inhibitor			
Vildagliptin (%)	13 (43.3%)	14 (48.3%)	0.796
Sitagliptin (%)	17 (56.7%)	15 (51.7%)	0.796
Prevalence of chronic complications			
Retinopathy # (%)	20.0	20.7	1.000
Nephropathy (%) (macroalbuminuria)	13.3	8.9	0.671
CV of ECG R-R intervals (%)	2.05(1.58: 3.31) (N = 21)	2.05(1.72: 2.70) (N = 24)	0.699
Macroangiopathy * (%)	33.3	37.9	0.793

Group A: individual group treated with DPP-4 inhibitor and glimepiride. Group G: individual group treated with DPP-4 inhibitor and gliclazide. eGFR: estimated glomerular filtration ratio. DPP-4: dipeptidyl peptidase-4. #: pre-proliferative or proliferative retinopathy. CV: coefficient of variation. ECG: electrocardiogram. *: coronary arterial disease, cerebrovascular disease, and/or peripheral arterial disease.

Blood glucose monitoring was performed using the previously mentioned FreeStyle LibrePro as an intermittent scan CGM. A sensor for glucose monitoring was attached to the upper arm, and blood glucose fluctuations were monitored every 15 min over a 10-day period (monitoring was conducted for 14 days, but values from the first 24 h and the last 2 days were considered unreliable [17,18]; therefore, values from 0:00 AM (midnight) on day 3 to 0:00 AM (midnight) on day 13 were used [17]. This system could monitor blood glucose levels from 40 mg/dL to 500 mg/dL. Hypoglycemia was defined as observing a monitoring value below 54 mg/dL [19] for 15 min or longer. As CGM metrics [20], we used the average monitored blood glucose value, Glucose Management Index (GMI), and time in target range. The time in target range (%) was indicated by the Time Above Range (TAR), Time in Range (TIR), and Time Below Range (TBR), where monitoring blood glucose levels were TAR: >180 mg/dL, TIR: 70–180 mg/dL, TBR: <70 mg/dL, TBR-level 1: 54–69 mg/dL, TBR-level 2: <54 mg/dL. Furthermore, the coefficient of variation (%CV)

and mean amplitude of glycemic excursions (MAGE) [21] were calculated as indices of monitoring blood glucose variability.

HbA1c was measured on the first day of monitoring. The 10-day observation period was divided into the following three types: whole-day (24 h), nighttime (midnight to 6:00 AM, 6 h) and daytime (6:00 AM to midnight, 18 h). Referencing the above CGM metrics, the frequency of individuals experiencing at least one episode of hypoglycemia during nighttime or daytime observation was compared between Groups A and G.

For an indicator of autonomic nervous system function, we employed the coefficient of variation in R-R intervals (CVRR) on a resting electrocardiogram, measured using a blood pressure pulse wave analysis device (Vs-3000TE: Fukuda Denshi Co., Ltd., Tokyo, Japan).

Results are presented as the median (25th percentile: 75th percentile). Where the median presentation was unclear (e.g., number of hypoglycemic episodes, SU drug dosage, TBR, TBR-level 1, TBR-level 2), the mean $\pm$ standard deviation is also shown in square brackets. Statistical testing used the Mann–Whitney U test was employed to evaluate differences between 2 groups for continuous variables. Fisher's exact test was used for testing significant differences in categorical variables between the two groups. Furthermore, for the logistic analyses, the explanatory variables were selected as the three confounding factors most likely associated with hypoglycemia: HbA1c, metformin use status, and type of SU drug. These analyses were performed using BellCurve for Excel Version 4.06 (Social Research Information Co., Ltd., Tokyo, Japan), with $p < 0.05$ considered statistically significant.

This study was approved by the Ethics Review Committee of Fuchu Hospital (Approval No. 2018017, Date: 12 October 2018). Written informed consent was obtained from all participants. This study is a retrospective observational study, and it was conducted in the outpatient department of our hospital between January 2019 and December 2020.

3. Results

The "Daily Record" was successfully filled out in detail by all participants. Everyone was living much the same as they had before monitoring, and no noteworthy entries were found. In particular, no association was found between alcohol consumption and nocturnal hypoglycemia. In two cases in Group G, the sensors became detached on the 12th day in both instances; however, 91.9% and 93.6% of the measurements, respectively, had been recorded during the 10-day period. Therefore, since more than 70% of the measurements were recorded in both cases [20], they were considered valid and included in the analysis data.

The frequency of participants who experienced hypoglycemia at least once during daytime or nighttime observation between Groups A and G is compared in Table 2. While no significant difference in the frequency of participants who experienced hypoglycemia in daytime observation was observed between them, the frequency of hypoglycemia during nighttime observation (nocturnal hypoglycemia) was significantly higher in Group A. Notably, 13 participants in Group A experienced nocturnal hypoglycemia at least once; the frequency ranged from 1 to 10 episodes over 10 days [4.2 ± 3.2] episodes/10 days. In Group G, only two patients experienced nocturnal hypoglycemia, with both participants having one episode per 10 days. Regarding hypoglycemia in daytime observation, 10 participants in Group A were observed, with a frequency ranging from 1 to 20 episodes per 10 days [4.4 ± 6.3] episodes/10 days, while eight participants in Group G were observed, with a frequency ranging from one to six episodes per 10 days [3.0 ± 1.9] episodes/10 days; no significant difference was observed between these frequencies ($p = 0.607$). No participants in either Group A or G reported clinical symptoms during nocturnal time. Additionally, hy-

poglycemia accompanied by clinical symptoms during daytime observation was confirmed in two participants in Group A and one participant in Group G (Table 2). When Groups A and G were combined, the CVRR for participants who experienced clinical symptoms during daytime hypoglycemia was $N = 3$, 3.31 (3.01:4.36), whereas the CVRR for participants without clinical symptoms was $N = 42$, 2.05 (1.66:3.14). Although a trend toward higher values was observed in participants with symptoms ($p = 0.075$), no statistically significant difference was found. Furthermore, no consistent pattern was observed regarding the time of day when hypoglycemia was observed.

Table 2. Comparison of individuals with hypoglycemia for more than one time between two groups.

Group	A (N = 30)	G (N = 29)	<i>p</i>
* Nighttime hypoglycemia			
Prevalence: number of individuals (%)	13 (43.3)	2 (6.9)	0.002
Frequency of hypoglycemia (times/10 days) in the individuals with hypoglycemia	4.2 ± 3.2	1 and 1	
Number of individuals with symptoms	0	0	
# Daytime hypoglycemia			
Prevalence: number of individuals (%)	10 (33.3)	8 (27.6)	0.779
Frequency of hypoglycemia (times/10 days) in the individuals with hypoglycemia	4.4 ± 6.3	3.0 ± 1.9	0.607
Number of individuals with symptoms	2 ^{\$}	1 &	

Group A: individual treated with DPP-4 inhibitor and glimepiride, Group G: individual treated with DPP-4 inhibitor and gliclazide, *: 0:00 AM (midnight) to 6:00 AM, (6 h), #: 6:00 AM to 0:00 AM (midnight) (18 h), \$: one individual had a mild headache before lunch and the other had a feeling of something being wrong before dinner. They recovered through dietary intake without any treatment. &: the individual had a mild headache before lunch. He recovered through dietary intake without any treatment.

The daily doses of SU are compared between individuals with and without nocturnal hypoglycemia in Table 3. No significant differences were observed in participants treated with both glimepiride and gliclazide.

Table 3. Comparison of dose of SU between individuals with and without nocturnal hypoglycemia.

SU	Glimepiride	Glimepiride	<i>p</i>	Gliclazide	Gliclazide	<i>p</i>
Hypoglycemia	(+)	(−)		(+)	(−)	
N	13	17		2	27	
Dose of SU (mg/day)	1.54 ± 0.56	1.21 ± 0.66	0.157	20 and 80	52.4 ± 26.4	

SU: sulfonylurea.

A comparison of CGM metrics between Groups A and G is shown in Table 4. While no monitoring glucose readings exceeding 500 mg/dL were observed, readings below 40 mg/dL were recorded 55 times in Group A (53 of which occurred during nighttime observation) and 2 times in Group G (one of which occurred at night). Monitored values below 40 mg/dL were calculated as 40 mg/dL. The mean monitored blood glucose levels and GMI were nearly equivalent in both groups, reflecting the trends in HbA1c. In both daytime and nighttime observations, the TBR and TBR-level 2 in Group A were significantly higher than those of Group G. In contrast, TIR in Group A was significantly lower than in Group G. In daytime observations, only TBR in Group A was significantly higher than in Group G; no significant differences were observed between the two groups for the other parameters. Across the three observation periods (Whole-day, nighttime, and daytime), the mean TBR in Group G was less than 4.0% in all cases, and the mean TBR-level 2 was also less than 1.0% in all cases. In contrast, the mean TBR for Group A exceeded 4.0% in 12 cases during both the whole-day and nighttime observations, and the mean TBR-level 2

also exceeded 1.0% in eight cases. Furthermore, in the whole-day observation, both %CV and MAGE were significantly higher in Group A. However, no significant difference was observed between Groups A and G in %CV during nighttime observation.

Table 4. Comparison of CGM metrics between two individual groups.

Group	A (N = 30)	G (N = 29)	p
* Whole-day glucose monitoring			
Average glucose (mg/dL)	147.6 (124.2:156.5)	138.7 (131.7: 153.6)	0.879
Glucose management indicator (%)	6.8 (6.3:7.1)	6.6 (6.5:7.0)	0.880
%CV (%)	36.1 (31.5:39.0)	30.6 (28.8:34.6)	0.002
MAGE (mg/dL)	122.1 (94.1:135.4)	98.8 (80.7:111.7)	0.012
TAR (%)	26.9 (17.9:32.5)	17.1 (13.0:29.2)	0.225
TIR (%)	68.4 (68.4:73.0)	78.4(68.3:83.6)	0.012
TBR (%)	3.0 (1.5:5.4) [6.5 ± 9.2]	0.4 (0:3.9) [2.2 ± 3.0]	0.007
TBR-level 1 (%)	2.1 (1.3:5.2) [4.7 ± 6.0]	0.4 (0:3.3) [1.9 ± 2.6]	0.009
TBR-level 2 (%)	0.2 (0:1.6) [1.8 ± 4.2]	0 (0:0.1) [0.2 ± 0.5]	0.021
# Nighttime glucose monitoring			
Average glucose (mg/dL)	107.0 (88.8:130.7)	109.7 (102.6:133.4)	0.317
%CV (%)	25.2 (18.4:30.2)	22.2 (18.6:24.8)	0.159
TAR (%)	1.5 (0:8.0)	2.9 (0:5.8)	0.582
TIR (%)	84.4 (68.5:93.6)	93.8 (83.8:96.3)	0.020
TBR (%)	4.6 (0.5:13.3) [15.5 ± 24.8]	1.3 (0:4.2) [3.6 ± 5.8]	0.030
TBR-level 1 (%)	3.1 (0.5:10.6) [10.4 ± 16.1]	1.3 (0:4.2) [3.5 ± 5.8]	0.056
TBR-level 2 (%)	0 (0:3.1) [5.0 ± 12.1]	0 (0:0) [0.1 ± 0.3]	<0.001
\$ Daytime glucose monitoring			
Average glucose (mg/dL)	158.8 (137.9:167.8)	145.3 (140.7:166.6)	0.682
%CV (%)	34.9 (29.5:36.8)	29.8 (26.6:32.0)	0.007
TAR (%)	34.3 (23.8:39.4)	22.8 (16.5:38.9)	0.237
TIR (%)	63.6 (59.5:70.8)	73.6 (60.8:82.3)	0.063
TBR (%)	2.0 (0.3:4.3) [3.7 ± 4.6]	0.4 (0:1.2) [1.7 ± 2.7]	0.025
TBR-level 1 (%)	1.7 (0.3:4.2) [2.5 ± 3.1]	0.4 (0:1.2) [1.4 ± 2.2]	0.021
TBR-level 2 (%)	0 (0:0.4) [0.8 ± 1.9]	0 (0:0.1) [0.3 ± 0.7]	0.285

Group A: individual treated with DPP-4 inhibitor and glimepiride, Group G: individual treated with DPP-4 inhibitor and gliclazide, CGM: continuous glucose monitoring, *: 24 h, #: 0:00 AM (midnight) to 6:00 AM (6 h), \$: 6:00 AM to 0:00 AM (midnight) (18 h), CV: coefficient of variation, MAGE: mean amplitude of glucose excursion, TAR: time above range (>180 mg/dL), TIR: time in range (70–180 mg/dL), TBR: time below range (<70 mg/dL), TBR-level 1: (54–69 mg/dL), TBR-level 2: (<54 mg/dL).

Logistic regression analysis with hypoglycemia observed during nighttime observation (participants with one or more episodes) as the dependent variable is shown in Table 5. The sulfonylurea (glimepiride) was identified as a significant predictor. Similarly, in logistic regression analysis with hypoglycemia during daytime observation as the dependent variable, the sulfonylurea was not a significant predictor, whereas HbA1c levels (low values) were significant predictors (Table 6).

Table 5. Logistic regression analysis for the * presence of hypoglycemia during # nighttime observation in individuals treated with DPP-4 inhibitor and sulfonylurea (0: absence of nocturnal hypoglycemia, 1: presence of nocturnal hypoglycemia).

Explanatory Variable	Standard Partial Regression Coefficient	Odds Ratio (95% CI)	p
HbA1c	−0.410	0.384 (0.079–1.859)	0.234
Concomitant use of metformin (0: without, 1: with)	0.424	2.711 (0.502–14.643)	0.247
Concomitant use of SU (1: glimepiride, 2: gliclazide)	−1.261	0.080 (0.015–0.429)	0.003

CI: confidence interval, odds ratio < 1.0: favors nocturnal hypoglycemia, *: on more than one time, #: 0:00 AM (midnight) to 6:00 AM (6 h), DPP-4: dipeptidyl peptidase-4, SU: sulfonylurea.

Table 6. Logistic regression analysis for the * presence of hypoglycemia during # daytime observation in individuals treated with DPP-4 inhibitor and sulfonylurea (0: absence of daytime hypoglycemia, 1: presence of daytime hypoglycemia).

Explanatory Variable	Standard Partial Regression Coefficient	Odds Ratio (95% CI)	p
HbA1c	−0.751	0.173 (0.039–0.770)	0.021
Concomitant use of metformin (0: without, 1: with)	−0.043	0.903 (0.224–3.634)	0.886
Concomitant use of SU (1: glimepiride, 2: gliclazide)	−0.093	0.831 (0.255–2.756)	0.762

CI: confidence interval, odds ratio < 1.0: favors daytime hypoglycemia, *: on more than one time, #: 6:00 AM to 0:00 AM (midnight) (18 h), DPP-4: dipeptidyl peptidase-4, SU: sulfonylurea.

4. Discussion

In this exploratory study, we used CGM to demonstrate for the first time that individuals with type 2 diabetes receiving combination therapy with a DPP-4 inhibitor and glimepiride experienced significantly more episodes of asymptomatic nocturnal hypoglycemia than individuals receiving combination therapy with a DPP-4 inhibitor and gliclazide. A “Daily Record” was filled out in detail by all participants, and no significant changes were observed in the patients during the period they wore the CGM. Furthermore, this study found no significant difference in GMI between the two groups, similar to the results for HbA1c; it is believed that the participants maintained the same level of glycemic control during the monitoring period as they had previously.

Cases of hypoglycemia associated with this combination therapy were reported in Japan shortly after DPP-4 inhibitors were first introduced into clinical practice [3]. Thus, sufficient attention has been paid to the risk of hypoglycemia throughout the history of this treatment. Specifically, regarding the dosage of SU drugs in combination therapy with DPP-4 inhibitors, the expert committee in this field strongly recommends reducing the dose of SU drugs, particularly for the elderly: glimepiride to 2.0 mg/day or less, and gliclazide to 40 mg/day or less [3]. The doses of glimepiride and gliclazide administered in this trial were $[1.4 \pm 0.6]$ mg/day and $[52.4 \pm 26.4]$ mg/day, respectively; the gliclazide dose was slightly higher than this recommendation. Furthermore, the presence or absence of metformin co-administration did not affect hypoglycemia (Tables 5 and 6). In this study, the mean TBR and TBR-level 2 values in Group G were less than 4% and less than 1%, respectively, across the three different observation periods. These results are all consistent with the evaluation criteria of international consensus recommendations (which recommend $TBR < 4\%$ and $TBR\text{-level } 2 < 1\%$ for non-pregnant adults with type 1 and type 2 diabetes in the hypoglycemic range [20]. In contrast, the mean TBR in Group A was significantly higher than that in Group G across all observation periods, and TBR-level 2 was also significantly higher in all observation periods. Furthermore, the mean TBR for both whole-day and the nighttime observations exceeded 4%. These results were consistent with the finding that hypoglycemia was observed more frequently in Group A than in Group G [20].

We used %CV as one of indicators of glycemic variability, it is generally accepted that a %CV exceeding 36% is associated with a significant increase in hypoglycemia [22]. In this study, the median %CV for Group A, which exhibited frequent hypoglycemia during the whole-day observation, was 36.1%, exceeding the 36% threshold. However, as no significant difference was observed between Groups A and G in the comparison of %CV during nighttime observation (Table 4), it was considered unlikely that nocturnal glycemic variability was associated with nocturnal hypoglycemia in Group A. It appears that blood glucose levels in Group A remained stable at a low level during the night, when

no food was consumed, and did not fluctuate significantly over the short 6 h period. We also employed MAGE as another indicator of glycemic variability. This metric is used to assess large fluctuations in monitoring glucose levels and is calculated solely based on whole-day monitoring glucose variability [21]. The authors have previously reported a study [23] comparing the frequency of nocturnal hypoglycemia in individuals with type 2 diabetes treated with insulin analogues based on the presence or absence of anti-insulin antibodies. In the antibody-negative group, nocturnal hypoglycemia was significantly more frequent and %CV was significantly higher than in the antibodies-positive group; however, no significant difference was observed in MAGE. In the present study, which examined individuals treated with oral medications (DPP-4 inhibitors and glimepiride) rather than insulin, Group A, which had a higher frequency of nocturnal hypoglycemia, showed significantly higher values not only for %CV but also for MAGE. This finding is consistent with a report [24] indicating that hypoglycemia tends to be more severe when caused by oral medications than when caused by insulin. In any case, since large fluctuations in monitoring glucose levels are thought to have a negative impact on chronic complications of diabetes [25], it appears necessary to closely monitor participants in Group A for chronic complications, especially macroangiopathy, in the future.

It is difficult to discuss that the frequency of nocturnal hypoglycemia is high in Group A based solely on these indicators of monitoring glucose variability; therefore, it was deemed necessary to consider other factors, such as the mechanisms of action and metabolism of oral medications. Unlike gliclazide, glimepiride binds to EPAC2A, which is localized in the incretin signaling pathway, and activates RAP1; it has been reported that when used in combination with DPP-4 inhibitors, it more potently amplifies insulin secretion from β -cells in response to glucose or sulfonylurea (SU) agents [26–28]. This potent insulin secretion-enhancing effect of DPP-4 inhibitors and glimepiride is considered to be one of the factors contributing to hypoglycemia. Furthermore, it has been reported that while glimepiride binds to two sites on the sulfonylurea receptor 1 (SUR1) in β -cells, gliclazide binds to only one site on SUR1; additionally, since the metabolites of glimepiride are active whereas those of gliclazide are inactive, glimepiride exhibits a longer-lasting insulin secretion-stimulating effect than gliclazide [29–31]. Considering these findings, the increased glycemic variability and prolonged insulin secretion-stimulating effect resulting from the combination of DPP-4 inhibitors and glimepiride might be thought to be associated with the higher incidence of nocturnal hypoglycemia in Group A compared to Group G, although the exact mechanism remains unclear at this time.

Despite 18 cases of hypoglycemia being observed during the day, clinical symptoms of hypoglycemia were rare. One possible cause is that many participants had a long duration of disease, with a median of approximately 15 years since diagnosis. The presence of concomitant autonomic neuropathy in such participants with a long duration may be a possible explanation, although no significant difference in CVRR was observed between the two groups with or without clinical symptoms of hypoglycemia.

Limitations of this study: Given that this is a single-center, single-race (Japanese), older adult, retrospective observational study with a relatively small sample size ($N = 59$), and considering the lack of strict dietary standardization, and potential inaccuracies in CGM data, further investigation is warranted for individuals showing significant differences between Groups A and G.

5. Conclusions

Among individuals with type 2 diabetes who had relatively good glycemic control, asymptomatic nocturnal hypoglycemia occurred more frequently in the group treated with a combination of a DPP-4 inhibitor and glimepiride than in the group treated with a

combination of a DPP-4 inhibitor and gliclazide. Even when HbA1c levels were comparable, the use of CGM clearly identified this difference.

Author Contributions: All authors contributed to the study conception and design. The idea of this study was conceived by T.S. CGM study and data analysis were performed by T.S., Y.M., S.Y. and Y.K. Calculation of CGM metrics from raw data obtained from CGM studies was performed by T.S. The first draft of the manuscript was written by T.S., and all authors commented on previous versions of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Fucho Hospital, Seichokai Social Medical Corporation (approval number: 2018017, date: 12 October 2018).

Informed Consent Statement: Informed consent was obtained in writing form from all participants.

Data Availability Statement: The data presented in this study are available on reasonable request.

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