[Original]

Comparison Between Effectiveness of 100 mg/day Sitagliptin and a Switch to Mitiglinide Calcium Hydrate/Voglibose from 50 mg/day Sitagliptin in Patients with Type 2 Diabetes

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Abstract **:** We analyzed the effects of 100 mg/day sitagliptin and a switch to mitiglinide calcium hydrate/voglibose compound tablets (MIT/VOG) in patients with type 2 diabetes mellitus (T2DM) treated with 50 mg/day sitagliptin. Five patients with T2DM treated with 50 mg/day sitagliptin and hemoglobin A1c (HbA1c) of ≥6.5% were switched to MIT/VOG, or the dose of sitagliptin was increased to 100 mg/day. The effects of the changes in therapy were compared in a crossover fashion by continuous glucose monitoring. The primary endpoint was mean amplitude of glycemic excursions (MAGE), and the secondary end points were 24-hour mean blood glucose level and mean blood glucose level from 0:00 a.m. to 7:00 a.m. and from 7:00 a.m. to 0:00 a.m., percentage of time with blood glucose level of ≥200 mg/d*l* and <70 mg/d*l*, maximum and minimum blood glucose levels, and increases in postprandial blood glucose levels. MAGE was significantly lower with MIT/VOG ($P = 0.016$), whereas mean blood glucose levels were lower between 0:00 a.m. and 7:00 a.m. with 100 mg/day sitagliptin. The percentage of time with blood glucose level ≥200 mg/d*l* was significantly shorter with MIT/VOG ($P = 0.041$). The maximum blood glucose level was significantly lower with MIT/VOG ($P = 0.043$), and the minimum was significantly lower with 100 mg/day sitagliptin ($P = 0.043$). Blood glucose levels after dinner and mean increases in postprandial blood glucose levels were significantly lower with MIT/VOG ($P = 0.090$ and $P = 0.045$ respectively). In patients with T2DM, treatment with MIT/VOG improves MAGE and postprandial hyperglycemia and 100 mg/day sitagliptin lowers early morning glucose levels. This trial was registered with the University Hospital Medical Information Network (UMIN) (No. UMIN R000008274).

Keywords **:** type 2 diabetes mellitus, sitagliptin, mitiglinide calcium hydrate/voglibose, continuous glucose monitoring system, mean amplitude of glycemic excursions.

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Introduction

Many large-scale clinical studies of patients with type 2 diabetes mellitus (T2DM) have shown the significance of improving not only hemoglobin A1c (HbA1c) values but also postprandial hyperglycemia without causing hypoglycemia or body weight gain in the control of macrovascular complications [1−4]. The

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Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) study of Asian subjects reported that, similar to European subjects, postprandial hyperglycemia significantly increased the risk of death compared with high fasting blood glucose levels [1], suggesting that strict control of postprandial hyperglycemia improves long-term prognosis [5]. Compared with Europeans and Americans, many Japanese patients with T2DM have lower insulin secretion capacity. This results primarily from insulin hyposecretion in the early stage, particularly for increases in postprandial blood glucose levels. Marked postprandial hyperglycemia is especially observed in patients with borderline and mild diabetes [6].

Dipeptidyl peptidase 4 (DPP-4) inhibitors selectively and reversibly inhibit DPP-4, a degrading enzyme of incretin, thereby stimulating incretin-mediated insulin secretion in a glucose-dependent manner through insulin secretion-promoting action in pancreatic β cells and glucagon inhibitory action in pancreatic α cells. DPP-4 inhibitors can lower blood glucose levels and improve postprandial blood glucose levels in particular [7, 8]. Administration of 50 mg sitagliptin, a DPP-4 inhibitor, significantly improves postprandial blood glucose levels, and a double dose can be administered when efficacy is less than ideal [9]. In addition, mitiglinide calcium hydrate/voglibose (MIT/VOG), a compound drug of the glinide agent mitiglinide and an α-glucosidase inhibitor (α-GI), potently improves postprandial blood glucose levels with different mechanisms of action [10, 11]. To our knowledge, however, there are no studies that have directly compared these drugs (e.g., double dose and switching to a compound tablet) in patients with poor response to 50 mg sitagliptin.

In the present study, patients with T2DM who were being treated with 50 mg sitagliptin and showed poorly controlled blood glucose levels were assigned to receive 100 mg sitagliptin or switched to MIT/VOG. Differences in the effects of these two drugs were analyzed in a crossover manner by using continuous glucose monitoring (CGM).

Subjects and Methods

Subjects

The subjects were 5 patients (4 men and 1 woman; age range, 20 to 79 years) with T2DM who were being treated with 50 mg sitagliptin at the University Hospital of Occupational and Environmental Health, Japan. Their HbA1c values were ≥6.5%, and no fluctuations in HbA1c values were recorded within 16 weeks after the start of 50 mg oral sitagliptin (range of HbA1c fluctuations, ≤0.5%). None of the patients was being treated with sulfonylurea drugs, α-GI, or glinide drugs; none developed diabetic ketoacidosis or diabetic coma during the study, had type 1 diabetes mellitus, had serious infection, underwent or was scheduled to undergo surgery, suffered major trauma, had moderate or severe renal disease (creatinine level ≥1.5 mg/d*l* for men and ≥1.3 mg/d*l* for women), or had liver disease (aspartate aminotransferase or alanine aminotransferase levels 3 times greater than normal); and for female patients: none was pregnant, possibly pregnant, or lactating during the course of the study. The required sample size was estimated using data from our CGM study. When the dose of sitagliptin was increased from 50 to 100 mg, mean amplitude of glycemic excursions (MAGE) was 104 mg/d*l*. When sitagliptin 50 mg was switched to MIT/VOG, MAGE was 42 mg/d*l*. Calculation of the sample size was based on a standard deviation of 38 mg/d*l* for both groups. The calculated minimum sample size was 7 patients for each group, with an α error of 0.05 and power of 80.0%.

Study design

The study protocol is shown in Fig.1. Each patient was assigned to either switch to treatment from 50 mg sitagliptin to MIT/VOG or an increase of the dose of sitagliptin to 100 mg/day. After treatment for 5 days, they were crossed over to the other treatment regimen. CGM was measured before drug administration and before and after the crossover to examine MAGE and standard deviation. Blood glucose markers were evaluated with CGM at day 5 of drug administration. Treatment was continued from the start of the intervention, and any new concomitant use or dose increase of an oral hypoglycemic agent was prohibited. During the intervention period, medications other than oral hypoglycemic agents were not changed unless required. The primary end point was MAGE, and the secondary end points were 24-hour mean blood glucose levels and mean blood glucose levels from 0:00 a.m. to 7:00 a.m.

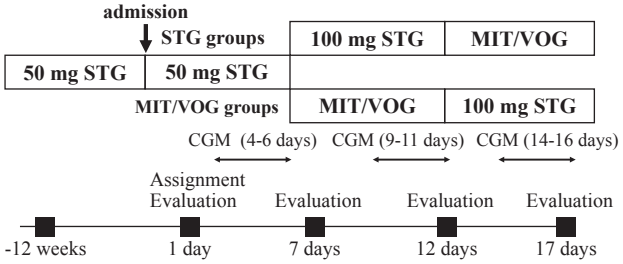

Fig. 1. Study protocol of comparison between effectiveness of 100 mg STG and switch to MIT/VOG. Subjects were switched to treatment with MIT/VOG, or the dose of STG was increased from 50 to 100 mg/day. After treatment for 5 days, they were crossed over to the other treatment regimen. Glycemic indices were examined before administration and before and after crossover by CGM. MIT: mitiglinide calcium hydrate, VOG: voglibose, STG: sitagliptin, CGM: continuous glucose monitoring system.

and from 7:00 a.m. to 0:00 a.m., percentage of time with blood glucose levels ≥200 mg/d*l* and <70 mg/d*l*, maximum and minimum blood glucose levels, blood glucose levels before each meal, and increases in postprandial blood glucose levels. It should be noted that, for meals, 25 kcal/kg standard body weight of diabetes food until the study was completed immediately after hospitalization (55% carbohydrate, 20% protein, 25% fat, salt 7g) was unified. This study was conducted with the approval of the Ethics Committee of the University of Occupational and Environmental Health, Japan. The subjects were provided with documents explaining the purpose of the study and gave informed consent to participate in the study.

Continuous glucose monitoring system

CGM was performed using a CGMS Gold (Medtronic Minimed, Northridge, CA, USA). The mean blood glucose level, standard deviation (SD), MAGE, percentage of time with glucose levels of <70, ≥140, and ≥200 mg/d*l* were measured from the data recorded through CGM using self-monitoring blood glucose (SMBG) device. MAGE, which was proposed by Service *et al*. [12], represents fluctuations in blood glucose levels over a 24-hour period and was calculated from the daily variations in blood glucose level, which was measured continuously by CGM over a period of 2 days. Previous studies indicated interstitial glucose concentrations measured by CGM correlate with venous blood glucose levels [13]. CGM measurements represent glucose concentrations in the interstitial fluid, but since the introduction of the SMBG technique, the measured value is considered to represent blood glucose level. SMBG was performed using a ONE TOUCH ULTRA VIEW (Johnson & Johnson K.K, Tokyo, Japan).

Laboratory evaluation

The value of HbA1c (%) was estimated as an National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) derived from the Japanese Diabetes Standardization (JDS) value and calculated by the formula HbA1c (%) = HbA1c (JDS) (%) + 0.4% [14]. Fasting blood glucose levels were measured by a standard enzymatic method. Venous blood samples were obtained in the morning following an overnight fast. Homeostasis model − assessment of insulin resistance (HOMA-IR) was calculated by the following formula: HOMA-IR = [fasting immunoreactive insulin (FIRI) (μU/*l*) × fasting blood glucose (mg/d*l*)/405].

Statistical analysis

Results were expressed as mean ± standard deviation. Comparison of two groups was performed using the Wilcoxon signed rank test. The Fisher's exact probability test was employed for categorical data. The odds ratio and 95.0% confidence interval were computed for all variables. A P value < 0.05 was considered significant. Analyses were performed with SPSS Statistical Software 21.0 (SPSS Inc. Chicago, IL).

Results

Baseline characteristics of patients

Two patients were switched from sitagliptin to MIT/VOG, and 3 patients were switched from MIT/VOG to sitagliptin. The mean age of the five patients was 66.2 ± 10.2 years, and the mean duration of T2DM was 22.4 ± 14.9 years. The mean body weight was 61.5 ± 11.6 kg, and mean body mass index was 23.0 ± 5.5 kg/m^2. Complications included neuropathies (60.0%), retinopathies (20.0%), and/or nephropathies (20.0%). The mean HbA1c value was 7.1% ± 0.2%, mean fasting plasma glucose (FPG) level was 126.8 ± 5.7 mg/d*l*, mean FIRI level was 6.8 ± 3.9 μU/m*l*, mean HOMA-IR was 2.1 ± 1.2, and mean urinary C-peptide immunoreactivity

Table 1. Baseline clinical characteristics of study participants with type 2 diabetes mellitus

STG → MIT/VOG (STG group) (n)		2
MIT/VOG → STG (MIT/VOG group) (n)		3
Sex (male, female)		4/1
Age (years)		66.2 ± 10.2
Duration of diabetes (years)		22.4 ± 14.9
Body weight (kg)		61.5 ± 11.6
Body mass index (kg/m^2)		23.0 ± 5.5
Complications (%)	neuropathies retinopathies nephropathies	60.0% 20.0% 20.0%
HbA1c (%)		7.1 ± 0.2
Fasting plasma glucose (mg/d*l*)		126.8 ± 5.7
FIRI (μU/m*l*)		6.8 ± 3.9
HOMA-IR		2.1 ± 1.2
u-CPR （μg/day）		78.6 ± 30.3

Data are mean ± SD. STG: sitagliptin, MIT: mitiglinide calcium hydrate, VOG: voglibose, FIRI: fasting immunoreactive insulin, HOMA-IR: homeostasis model assessment-insulin resistance, u-CPR: urinary-C-peptide immunoreactivity

was 78.6 ± 30.3 μg/day (Table 1). None of the patients experienced adverse reactions.

Changes in indices of glycemic control

MAGE was significantly lower with MIT/VOG compared with sitagliptin (Fig. 2). Figure 3 shows a representative CGM trace. Treatment with either drug did not lower blood glucose level to <70 mg/d*l*, and the percentage of time spent at blood glucose levels of ≥200 mg/d*l* was significantly shorter with MIT/VOG (Table 2). Although there were no significant differences in 24-hour mean blood glucose levels and mean blood glucose from 0:00 a.m. to 7:00 a.m. and from 7:00 a.m. to 0:00 a.m., the mean blood glucose levels from 0:00 a.m. to 7:00 a.m. tended to be lower with 100 mg sitagliptin. Moreover, maximum blood glucose levels were lower with MIT/VOG, and minimum blood glucose levels were lower with 100 mg sitagliptin (Table 2). Increases in blood glucose levels after breakfast and lunch showed no difference between the 2 drugs; however, increases in blood glucose levels after dinner and mean increases in postprandial blood glucose levels were significantly lower with MIT/VOG (Table 3).

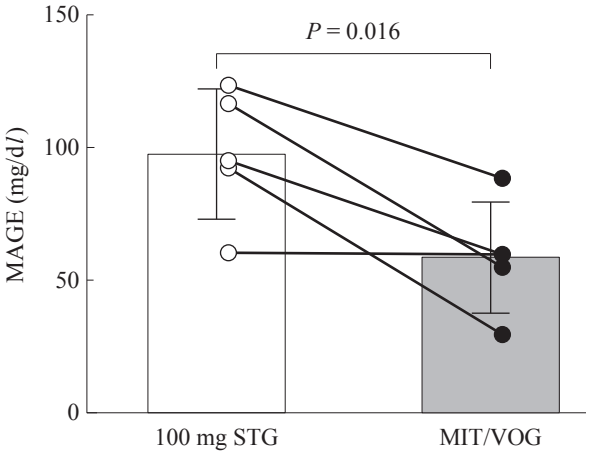

Fig. 2. Effects of MIT/VOG and 100 mg STG on MAGE. Data are mean ± SD. $P < 0.05$, by Mann-Whitney U test. MIT: mitiglinide calcium hydrate, VOG: voglibose, STG: sitagliptin, MAGE mean amplitude of glycemic excursions.

Table 2. Blood glucose levels while being treated with 100 mg STG or MIT/VOG

blood glucose level	100 mg STG	MIT/VOG	*p* value
A. Percentage of time			
≥ 200 mg/d*l*	10 ± 10	1 ± 3	0.041
≥ 140 mg/d*l*	37 ± 23	36 ± 23	0.917
<70 mg/d*l*	0 ± 0	0 ± 0	1.000
B. CGM parameters			
24-hour (mean)	140 ± 14	136 ± 14	0.602
From 0:00 a.m. to 7:00 a.m. mean	113 ± 8	122 ± 9	0.076
From 7:00 a.m. to 0:00 a.m. mean	151 ± 23	142 ± 17	0.465
Standard deviation	33 ± 11	20 ± 8	0.080
Maximum	226 ± 21	187 ± 34	0.043
Minimum	91 ± 9	105 ± 12	0.043
Before breakfast	118 ± 18	119 ± 7	1.000
Before lunch	127 ± 20	126 ± 13	0.893
Before dinner	113 ± 9	129 ± 30	0.144

A: Data show percentage of time of blood glucose levels while being treated with 100 mg STG or MIT/VOG. B: Data show blood glucose levels of CGM parameters while being treated with 100 mg STG or MIT/VOG. Data are mean ± SD, CGM: continuous glucose monitoring system, STG: sitagliptin, MIT: mitiglinide calcium hydrate, VOG: voglibose

Table 3. Increase in postprandial blood glucose levels (mg/d*l*) while being treated with 100 mg STG or MIT/VOG

Measurement period of blood glucose level	100 mg STG	MIT/VOG	*p* value
After breakfast	71 ± 37	51 ± 23	0.347
After lunch	56 ± 22	34 ± 21	0.173
After dinner	108 ± 17	58 ± 17	0.009
Average	79 ± 19	48 ± 16	0.045

Data are mean ± SD. STG: sitagliptin, MIT: mitiglinide calcium hydrate, VOG: voglibose

Discussion

Treatment of patients with T2DM has improved after the launch of new oral hypoglycemic agents, but many treatment-related issues remain less than ideal, such as insufficient glycemic control, adverse reactions (e.g., hypoglycemia and body weight gain), and progressive islet dysfunction. Large-scale clinical studies [1−4] have proposed the selection of treatment for diabetes that can improve HbA1c value without causing hypoglycemia or body weight gain, and at the same time take into consideration postprandial hyperglycemia and fluctuations in blood glucose levels.

Incretin stimulates blood glucose–dependent insulin secretion and has a glucagon secretion inhibitory action (incretin effect); it binds to receptors on β cells and increases intracellular cyclic adenosine monophosphate levels, and also enhances exocytosis of insulin secretory granules by calcium through a protein kinase A−dependent pathway or a protein kinase A−independent pathway mediated by Epac (cAMP-GEFII) [15]. The DPP-4 inhibitor sitagliptin enhances insulin secretion through inhibition of incretin degradation and suppresses elevation of blood glucose levels through inhibition of glucagon secretion [16, 17]. In addition, sitagliptin has been reported to improve blood glucose levels in a dose-dependent manner [9]. On the other hand, MIT/VOG provides strict postprandial glycemic control in a synergetic manner through different actions of the two drugs; mitiglinide improves the early-stage postprandial insulin secretory response towards a physiological pattern, while voglibose delays the absorption of glucose from the small intestine [18, 19].

Baseline laboratory tests in our patients showed HbA1c of approximately 7.0%, FPG of approximately 120 mg/d*l*, mild insulin resistance, HOMA-IR of 2.1, and adequate insulin secretion and urinary C-peptide immunoreactivity of 78.6 μg/day. Treatment with the two drugs did not change 24-hour mean blood glucose level or mean blood glucose level from 0:00 a.m. to 7:00 a.m. and from 7:00 a.m. to 0:00 a.m. However, mean blood glucose levels from 0:00 a.m. to 7:00 a.m. tended to be lower with 100 mg sitagliptin, and minimum blood glucose levels were also lower with 100 mg sitagliptin. As reported previously, this result shows suppression of the dawn phenomenon by the glucagon secretion inhibitory effect of sitagliptin from midnight to early morning [20]. These results suggest that sitagliptin has a better improvement effect in the fasting state in the early morning than MIT/VOG.

Our results suggest that MIT/VOG is more effective than increasing the dose of sitagliptin to 100 mg because 1) MAGE was significantly lower with MIT/VOG; 2) the percentage of time spent with blood glucose levels at ≥200 mg/d*l* was significantly shorter with MIT/VOG; and 3) despite the lack of difference in increases in blood glucose levels after breakfast and lunch, increases in blood glucose levels after dinner and mean increases in postprandial blood glucose levels were significantly lower with MIT/VOG. Both SD and MAGE are indicators reflecting postprandial hyperglycemia, but MAGE sees blood glucose fluctuation above 1 SD and is considered to reflect more postprandial hyperglycemia. Therefore, we considered that MAGE was likely to make a more significant difference than SD. In this regard, postprandial hyperglycemia is considered to be due to the synergetic effects of gradual glucose absorption of α-GI and improvement of early-stage insulin secretion by glinide [21]. As it has been reported that MIT/VOG improves glycemic control in terms of medication adherence [22], the use of MIT/VOG, which is considered to act as both α-GI and glinide, is considered significant.

One article reporting on CGM showed that mean 24-h blood glucose, MAGE, highest blood glucose level after supper, and hyperglycemia after breakfast were significantly lower in patients with T2DM taking vildagliptin 100 mg/day than those taking sitagliptin 50 mg/day [23]. If vildagliptin 100 mg/day had been used in the present study, the difference in the glucose

level after dinner might have been small.

This study showed that switching to MIT/VOG is effective in patients treated with 50 mg sitagliptin who have favorable early morning fasting blood glucose levels but experience postprandial hyperglycemia. On the other hand, increasing the dose of sitagliptin to 100 mg is expected to be effective in patients with poorly controlled early morning fasting blood glucose levels (Fig. 3). DPP-4 inhibitors can now be combined with MIT/VOG, and the combination reportedly further improves postprandial blood glucose levels [24]. Therefore, it will be advantageous to increase the dose of sitagliptin to 100 mg and combine it with MIT/VOG to enhance treatment efficacy in patients with poorly controlled early morning fasting blood glucose levels and postprandial hyperglycemia.

This study has several limitations. First, the subjects in this study were inpatients. We have reported that diet therapy improves circadian variations in blood glucose levels within a few days after admission and that circadian variations are dissociated from HbA1c values in CGM. Accordingly, a study that includes outpatients may have a different outcome. Second, this study included a small sample size; the results should be verified in a larger sample size. The reasons for the small sample were as follows: 1) Many of our outpatients with diabetes were using sitagliptin 50 mg in combination with sulfonylurea (SU), α-GI, glinide, or insulin; 2) some of the patients with HbA1c levels of 6.5−8.0% preferred to be treated as outpatients rather than inpatients. For example, one patient requested discharge from our hospital after achieving good blood glucose control and thus withdrew from the study (group B). 3) Two patients with HbA1c levels ≥ 9.0% were withdrawn from the study because insulin therapy was necessary to reverse glucose toxicity (1 patient each in groups A and B).

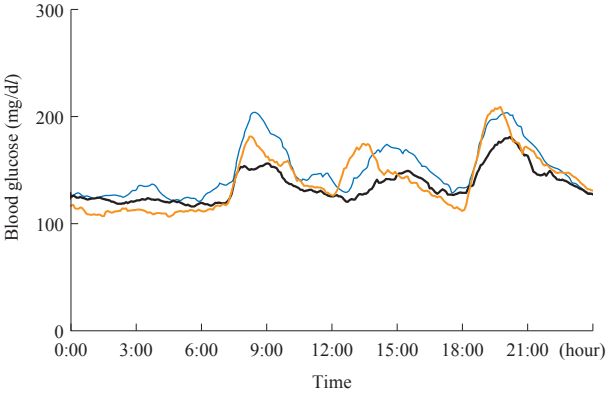

Fig. 3. CGM trace of a representative patient. Switching to MIT/VOG was effective in patients treated with 50 mg STG who had favorable early morning fasting blood glucose levels but experienced postprandial hyperglycemia. Increasing the dose of STG to 100 mg is expected to be effective in patients with poorly controlled early morning fasting blood glucose levels. CGM: continuous glucose monitoring system, MIT: mitiglinide calcium hydrate, VOG: voglibose, STG: sitagliptin. —: STG 50 mg, —: MIT/VOG, —: STG 100 mg.

In conclusion, switching to MIT/VOG improved fluctuations in blood glucose levels and postprandial hyperglycemia. In addition, increasing the dose of sitagliptin to 100 mg/day reduced blood glucose levels from midnight to early morning in patients with postprandial hyperglycemia and HbA1c values of approximately 7.0%, FPG levels of approximately 120 mg/d*l*, and postprandial glucose levels of ≥200 mg/d*l*.

Conflicts of Interest

Y. Tanaka has received consulting fees, speaking fees, and honoraria from MSD. Y. Okada has received consulting fees, lecture fees, and honoraria from MSD, and KISSEI. T. Arao, K. Torimoto, K. Sugai, T. Otsuka and A. Kurozumi have no conflicts of interest.

Acknowledgments

We thank Ms. N. Sakaguchi for her expert technical assistance.

Human Rights Statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed Consent

Informed consent or a substitute for it was obtained from all patients for being included in the study.

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2型糖尿病患者におけるシタグリプチン50 mgから100 mgへの増量とミチグリニドカルシウム水和物・ボグリボースへの切り替えにおける有用性に関する比較検討

新生　忠司[1,2]，岡田　洋右[2]，鳥本　桂一[2]，須貝　慧[2]，大塚　隆史[2]，黒住　旭[2]，田中　良哉[2]

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要　　旨：シタグリプチン（sitagliptin; S）50 mgで効果不十分な2型糖尿病患者をS 100 mgに増量する群とミチグリニドカルシウム水和物・ボグリボース（mitiglinide calcium hydrate/ voglibose）配合錠（M/V）に変更する群とに分け，両薬剤の特徴や差異を明らかにする．S 50 mgにて加療中のHbA1c 6.5%以上の2型糖尿病患者5名にM/Vに切替群，S 100 mg増量群に無作為に割り付け，5日間投与後にクロスオーバーを行う．主要評価項目は，平均血糖変動幅（MAGE），副次評価項目は24時間平均血糖，血糖200 mg/d*l*以上，70 mg/d*l*未満出現頻度，午前0時～午前7時平均血糖，午前7時～午前0時平均血糖，最大血糖，最小血糖，各食前血糖，食後血糖上昇幅とした．MAGEは，M/Vで$P = 0.016$と有意に低かった．24時間平均血糖，午前0時～午前7時平均血糖，午前7時～午前0時平均血糖に差は無かったが，午前0時～午前7時平均血糖はS 100 mgで低い傾向が見られた．血糖70 mg/d*l*未満はなく，血糖200 mg/d*l*以上の時間はM/Vで$P = 0.041$と有意に短かった．最大血糖はM/Vで$P = 0.043$と有意に低く，最小血糖はS 100 mgで$P = 0.043$と有意に低かった．朝食後，昼食後血糖上昇幅に差はないが，夕食後と平均の食後血糖上昇幅はM/Vで各々$P = 0.090, 0.045$と有意に低かった．2型糖尿病患者では，M/Vへの変更で平均血糖変動幅や食後高血糖が改善し，S 100 mgへの増量では深夜から早朝の血糖が低下する特徴が明らかになった．この研究は，大学病院医療情報ネットワーク（UMIN）に登録された（No.UMIN R000008274）．

キーワード：2型糖尿病，シタグリプチン，ミチグリニドカルシウム水和物・ボグリボース，持続的グルコースモニタリングシステム，平均血糖変動幅．

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