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ORIGINAL ARTICLE

Relationship between glycated hemoglobin level and duration of hypoglycemia in type 2 diabetes patients treated with sulfonylureas: A multicenter cross-sectional study

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ABSTRACT

Aims/Introduction: Sulfonylurea-related hypoglycemia increases the risk of cardiovascular sequela, such as cardiac arrhythmia. This study aimed to clarify the relationship between the level of glycated hemoglobin (HbA_{1c}) and the duration of hypoglycemia in type 2 diabetes patients treated with sulfonylureas.

Materials and Methods: Glucose levels in the enrolled patients (n = 300) were investigated with a professional continuous glucose monitoring device in the outpatient setting at six diabetes centers in Japan.

Results: A total of 269 participants completed the study. The duration of hypoglycemia with glucose values of <54 mg/dL was significantly longer in patients with an HbA_{1c} level of ≤6.4% than in those with an HbA_{1c} level of ≥8.0%, and that of hypoglycemia with glucose values of <70 mg/dL was significantly longer in patients with an HbA_{1c} level of ≤6.4%, 6.5–6.9% or 7.0–7.4% than in those with an HbA_{1c} level of ≥8.0%. Patients with an HbA_{1c} level of ≤6.4% were exposed to glucose values of <70 mg/dL for >10% of the time in daily life (6.8 ± 5.6 min/h). The duration of hypoglycemia with glucose values of <70 mg/dL was longer at night than during the daytime, and the nadir of glucose values occurred between 03.00 and 05.00 hours irrespective of HbA_{1c} level. The duration of hypoglycemia was associated with the duration of diabetes and sulfonylurea dose.

Conclusions: The duration of hypoglycemia was inversely correlated with HbA_{1c} level and was longer during the night-time than daytime in type 2 diabetes patients treated with sulfonylureas.

INTRODUCTION

Hypoglycemia is one of the most frequent adverse events in the treatment of diabetes. It not only triggers unpleasant symptoms and, in severe cases, disturbed consciousness, but also exerts exacerbating effects on various conditions associated with diabetes, including microvascular complications, cardiovascular events, cognitive disorders and shortening of lifespan[1–3].

Sulfonylureas, the oldest class of oral glucose-lowering drugs, are still widely administered around the world because of their potent glucose-lowering effect and low cost. These drugs frequently trigger hypoglycemia, however, particularly in individuals with low levels of glycated hemoglobin (HbA_{1c})[4,5]. Evidence suggests that sulfonylurea-related hypoglycemia increases the risk of cardiovascular sequela, such as cardiac arrhythmia[6]. A large database analysis showed that the lowest hazard ratio for mortality was apparent at an HbA_{1c} level of approximately 7.5% for patients with type 2 diabetes treated with

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sulfonylureas, with lower levels of HbA_{1c} being associated with increased mortality[7], suggesting that sulfonylurea-induced hypoglycemia occurs more frequently in individuals with lower levels of HbA_{1c} and leads to the increase in mortality. Information on the relationship between HbA_{1c} levels and the frequency of hypoglycemia in patients treated with sulfonylureas is limited, however.

Continuous glucose monitoring (CGM), which provides a comprehensive picture of glycemic profile, has brought great advantages for the evaluation and control of glycemia in diabetes patients[8]. For the evaluation of hypoglycemia, CGM allows quantitative assessment of the frequency, duration and severity of the event. Furthermore, such devices are useful for the detection of unrecognized or nocturnal episodes of hypoglycemia[9,10], which are likely related to unfavorable outcomes in the treatment of diabetes[11,12]. As far as we are aware, however, the relationship between HbA_{1c} levels and the duration of hypoglycemia in individuals treated with sulfonylureas has not been examined with the use of CGM. We therefore designed a multicenter, cross-sectional study with a large number of study participants (n = 300) to gain insight into the relationship between HbA_{1c} levels and the duration of hypoglycemia in sulfonylurea-treated type 2 diabetes patients with a professional CGM system.

METHODS

Study design and participants

This multicenter, cross-sectional study was carried out at six diabetes centers in Japan. Potentially eligible patients at each study site were invited to participate in the study. A total of 300 participants who had visited the study sites as outpatients between September 2017 and January 2018, been diagnosed with type 2 diabetes, and treated with sulfonylureas, but not with insulin, were enrolled. Patients were excluded if they were aged <20 years or had an HbA_{1c} level of ≥12%. The protocol for the study was approved by the institutional review boards of the participating centers, and the study was carried out in accordance with the Declaration of Helsinki and its amendments. Written informed consent was obtained from all participants. The study was registered with the University Hospital Medical Information Network (UMIN000025284).

Procedures

All participants wore a FreeStyle Libre Pro sensor (Abbott Diabetes Care, Alameda, CA, USA) for 14 days. We analyzed CGM data of patients for whom at least 7 days of recorded data were available. We excluded data for the first day of wearing the device from analysis because of concerns about the accuracy of the CGM system during this initial period[13]. The CGM data were analyzed with the use of the device software (FreeStyle Libre Software, Abbott Diabetes Care; https://www.myfreestyle.com/provider, accessed 11 April 2016). All participants were asked to report hypoglycemic events and to evaluate the pain or itching associated with sensor insertion or wear according to a 5-point scale (1, none; 2, almost none; 3, mild; 4, moderate; 5, severe).

Outcomes

The primary outcome of the study was the difference in the duration of hypoglycemia (<54 or <70 mg/dL) between HbA_{1c} levels of ≥8.0% and either ≤6.4%, 6.5–6.9%, 7.0–7.4% or 7.5–7.9%. We also analyzed the 24-h glucose profile for each HbA_{1c} group, the difference in the duration of hypoglycemia (<54 or <70 mg/dL) between daytime (between 07.00 and 23.00 hours) and night-time (between 23.00 and 07.00 hours) for each HbA_{1c} group, and the association between the duration of hypoglycemia and age, the duration of diabetes, renal function, body mass index (BMI), diabetic complications, dose of sulfonylurea, and concomitant antidiabetic medications. Furthermore, we analyzed the differences in the mean glucose level, duration of hyperglycemia (≥180 mg/dL), time in the target glucose range (70–<180 mg/dL), standard deviation (SD) of 24-h glucose values, mean amplitude of glycemic excursions (MAGE), and the coefficient of variation of glucose levels between an HbA_{1c} level of ≥8.0% and the other HbA_{1c} groups. Safety end-points were the frequency of severe hypoglycemia (requiring third-party assistance) during CGM wear and symptoms related to sensor insertion or wear.

Statistical analysis

We calculated that a sample size of 285 was required to provide 80% power for detection of a difference between the

Table 1 | Baseline characteristics of the study patients

Characteristic	
Male/female	182/87
Age (years)	69.0 ± 10.7
BMI (kg/m^2)	24.6 ± 4.4
HbA_{1c} (%)	7.2 ± 0.8
eGFR (mL/min/1.73 m^2)	67.1 ± 22.5
Duration of diabetes (years)	17.5 ± 9.1
Diabetic retinopathy (none/SDR/ PPDR/PDR/unknown)	173/55/7/26/8
Diabetic nephropathy (stage 1/2/3/4)	166/75/22/ 6
Diabetic neuropathy	102
Macrovascular complications	69
Gliclazide/glimepiride/glibenclamide	85/168/16
Other antidiabetic agents (DPP-4 inhibitors/ biguanides/ thiazolidinediones/α-glucosidase inhibitors/SGLT-2 inhibitors/GLP-1 receptor agonists)	224/183/40/78/36/18

Total n = 269. Data are n or mean ± standard deviation values. BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; SDR, simple diabetic retinopathy; SGLT-2, sodium–glucose cotransporter 2.

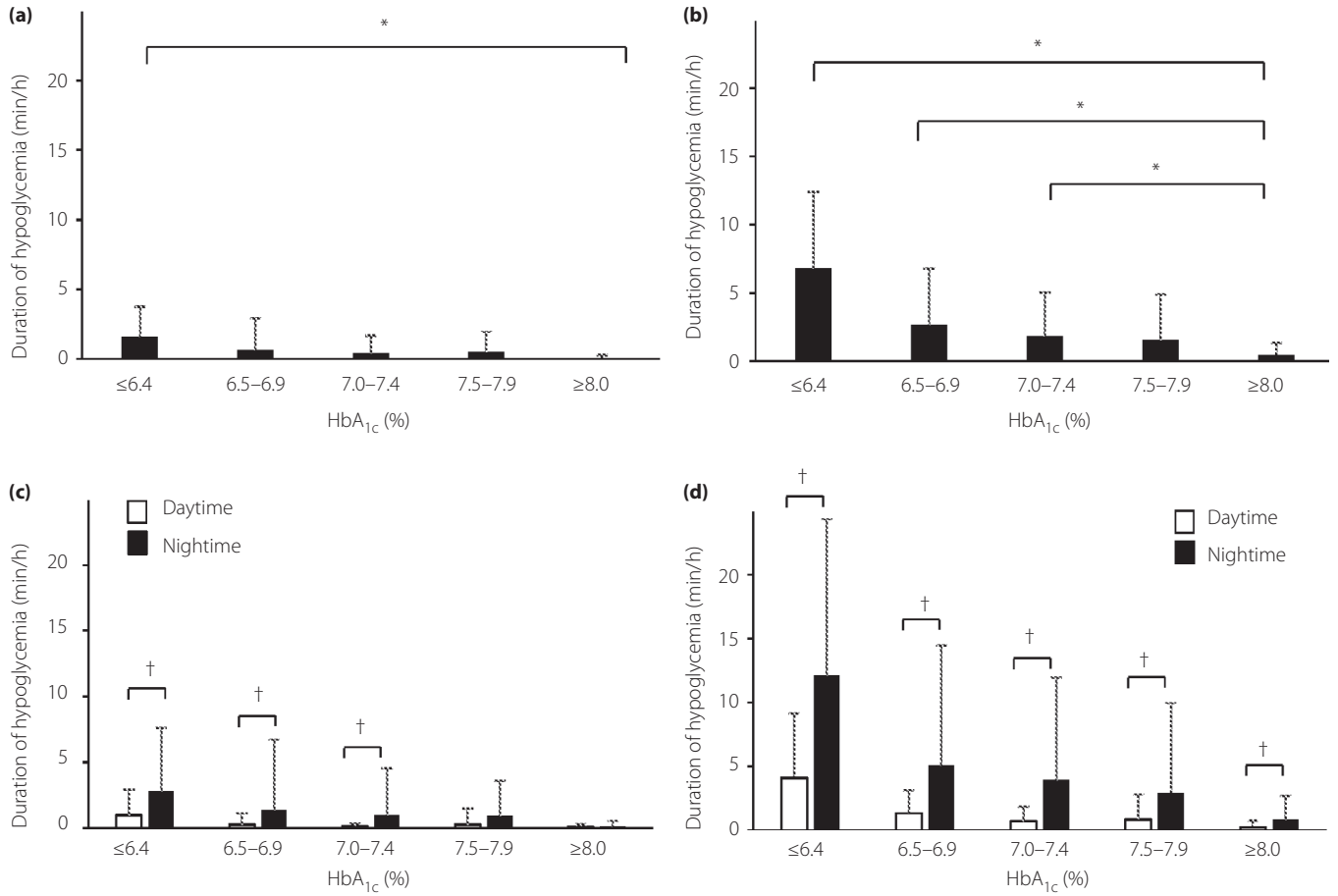

Figure 1 | Duration of hypoglycemia according to glycated hemoglobin (HbA_{1c}) level. (a) Duration of hypoglycemia with glucose values of <54 mg/dL. (b) Duration of hypoglycemia with glucose values of <70 mg/dL. (c) Duration of hypoglycemia with glucose values of <54 mg/dL during the daytime and night-time. Daytime: between 07.00 and 23.00 hours. Night-time: between 23:00 and 07:00 hours. (d) Duration of hypoglycemia with glucose levels of <70 mg/dL during the daytime and night-time. All data are the mean ± standard deviation. *$P < 0.0125$, †$P < 0.05$ (unpaired Student's *t*-test).

highest HbA_{1c} group and the other groups for the primary end-point with a two-sided significance level of 0.0125 (=0.05/4), as previously described[4,14]. Allowing for a dropout rate of 5%, a total of 300 participants was adopted for recruitment. We assessed the primary end-point with the unpaired Student's *t*-test, with a *P*-value <0.0125 being considered significant after application of Bonferroni's correction. Comparison of daytime and nocturnal hypoglycemia, as well as comparison of the mean glucose level, duration of hyperglycemia, time in the target glucose range, SD of 24-h glucose values, MAGE and CV of glucose levels among HbA_{1c} groups were also carried out with the unpaired Student's *t*-test, and with a *P*-value of <0.05 and <0.0125, respectively, being considered significant. Analysis of covariance was applied with adjustment for HbA_{1c} level to compare the duration of hypoglycemia between subgroups based on age (≥75 vs <75 years), duration of diabetes (≥15 vs <15 years), renal function (estimated glomerular filtration rate [eGFR] of ≥60 vs <60 mL/min/1.73 m^2), BMI (≥25 vs <25 kg/m^2), dose of sulfonylurea (high vs low dose relative to the median) or concomitant antidiabetic medications (plus vs minus dipeptidyl peptidase-4 [DPP-4] inhibitors or glucagon-like peptide-1 [GLP-1] receptor agonists; biguanides; thiazolidinediones; sodium–glucose cotransporter 2 inhibitors; or alpha-glucosidase inhibitors). Mean glucose levels and glycemic variability (SD of 24-h glucose values, MAGE and CV) were calculated with the use of EASY GV software (Nuffield Department of Primary Care Health Sciences, The University of Oxford, Oxford, UK)[15]. All statistical analysis was carried out with SPSS software version 22 (IBM SPSS Statistics, IBM Corp, Armonk, NY, USA).

RESULTS

Among the 300 enrolled patients, 25 individuals had CGM data for <7 days, and six lost their CGM sensors. A total of 269 participants who completed the study were thus included in

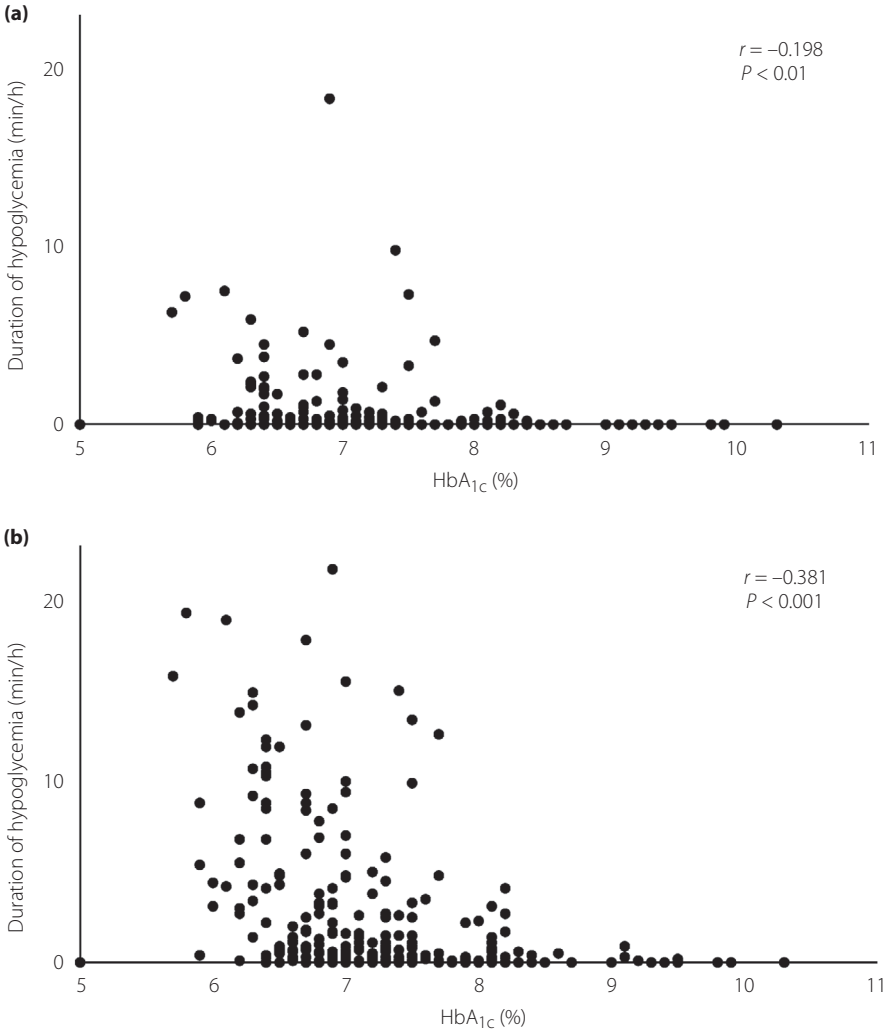

Figure 2 | Correlation between glycated hemoglobin (HbA_{1c}) level and duration of hypoglycemia. There was an inverse correlation between the duration of hypoglycemia with glucose levels of (a) <54 mg/dL or (b) <70 mg/dL and HbA1c level after adjustment for age, duration of diabetes, body mass index and estimated glomerular filtration rate.

the analysis. The baseline characteristics of the participants are shown in Table 1. A total of 38 (14%), 73 (27%), 69 (26%), 38 (14%) and 51 (19%) patients had HbA_{1c} levels of ≤6.4%, 6.5–6.9%, 7.0–7.4%, 7.5–7.9% and ≥8.0%, respectively. A total of 85, 168 and 16 patients were treated with gliclazide, glimepiride and glibenclamide, respectively, with total (mean ± SD) daily doses of 27.3 ± 18.4 mg, 1.1 ± 0.76 mg and 3.3 ± 2.0 mg, respectively.

The duration of hypoglycemia with glucose levels <54 mg/dL was 1.6 ± 2.2, 0.6 ± 2.3, 0.4 ± 1.3, 0.5 ± 1.5 and 0.1 ± 0.2 min/h for patients with HbA_{1c} levels of ≤6.4%, 6.5–6.9%, 7.0–7.4%, 7.5–7.9% and ≥8.0%, respectively, and was significantly ($P < 0.0125$) longer in the HbA_{1c} ≤6.4% group than in the ≥8.0% group (Figure 1a). The duration of hypoglycemia with glucose values of <70 mg/dL was 6.8 ± 5.6, 2.6 ± 4.1, 1.8 ± 3.2, 1.6 ± 3.3 and 0.4 ± 0.9 min/h for HbA_{1c} levels of ≤6.4%, 6.5–6.9%, 7.0–7.4%, 7.5–7.9% and ≥8.0%, respectively, and was significantly ($P < 0.0125$) longer in the HbA_{1c} ≤6.4%, 6.5–6.9% and 7.0–7.4% groups than in the ≥8.0% group (Figure 1b). The duration of hypoglycemia with glucose values of <54 mg/dL ($r = -0.198$, $P < 0.01$) or <70 mg/dL ($r = -0.381$, $P < 0.001$) was inversely correlated with HbA_{1c} levels after adjustment for age, duration of diabetes, BMI and eGFR (Figure 2).

The duration of hypoglycemia with glucose values of <54 mg/dL at night-time was significantly ($P < 0.05$) longer than that in the daytime for patients with HbA_{1c} levels of ≤6.4%, 6.5–6.9% or 7.0–7.4% (Figure 1c), whereas the duration of hypoglycemia with glucose values of <70 mg/dL at night-time was significantly longer than that in the daytime for all HbA_{1c} groups (Figure 1d). The mean 24-h glucose profiles determined for each HbA_{1c} group are shown in Figure 3. The nadir of glucose levels was apparent between 03.00 and 05.00 hours irrespective of HbA_{1c} level.

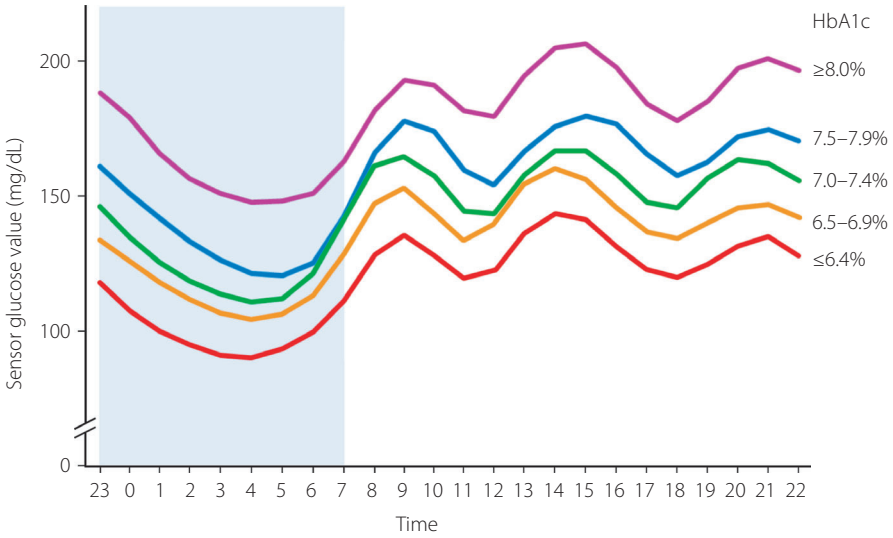

Figure 3 | The mean 24-h glucose profiles over 24 h according to glycated hemoglobin (HbA_{1c}) level. The nadir of glucose levels was apparent between 03.00 and 05.00 hours irrespective of HbA_{1c} level.

The duration of hypoglycemia with glucose values <70 mg/dL tended to be longer in patients aged ≥75 years than in those who were younger (3.0 vs 2.2 min/h, $P = 0.09$) after adjustment for HbA_{1c} levels (Table 2). The duration of hypoglycemia with glucose values of <54 or <70 mg/dL was significantly longer in patients with a diabetes duration of ≥15 years than in those with a shorter disease duration (0.80 vs 0.29 min/h, $P < 0.05$, and 3.0 vs 1.7 min/h, $P < 0.01$, respectively). The duration of hypoglycemia with glucose values of <70 mg/dL tended to be longer in patients with an eGFR of <60 mL/min/1.73 m^2 than in those with an eGFR of ≥60 mL/min/1.73 m^2 (3.1 vs 2.1 min/h, $P = 0.06$). The duration of hypoglycemia with glucose values of <54 or <70 mg/dL was similar between patients with a BMI of <25 or ≥25 kg/m^2. There were no significant differences in the duration of hypoglycemia between patients with or without diabetic retinopathy, nephropathy and neuropathy, as well as macrovascular complications (Table 2).

We also analyzed the relationship between sulfonylurea dose and the duration of hypoglycemia after adjustment for HbA_{1c} level (Table 2). Given that the median dose for gliclazide and glimepiride was 20 and 1 mg/day, respectively, we defined low and high doses of these drugs as ≤20 and >20 mg/day for gliclazide, and as ≤1 and >1 mg/day for glimepiride, respectively. We did not analyze the data for glibenclamide because of the small number of participants taking this drug. The duration of hypoglycemia with glucose values <54 or <70 mg/dL was significantly longer in patients treated with the high dose of each drug than in those treated with the low dose (gliclazide and <54 mg/dL, 0.84 vs 0.23 min/h, $P < 0.05$; gliclazide and <70 mg/dL, 4.2 vs 1.6 min/h, $P < 0.01$; glimepiride and <54 mg/dL, 1.5 vs 0.42 min/h, $P < 0.01$; and glimepiride and <70 mg/dL, 4.2 vs 1.8 min/h, $P < 0.01$).

The mean glucose level over a 24-h period was significantly ($P < 0.0125$) higher, the duration of hyperglycemia (≥180 mg/dL) was significantly longer and the time in the target glucose range (70 to <180 mg/dL) was significantly shorter in the HbA_{1c} ≥8.0% group than in each of the other four HbA_{1c} groups (Table 3). The SD of 24-h glucose values and MAGE were significantly higher, and the CV of glucose levels was significantly smaller in the HbA_{1c} ≥8.0% group than in the ≤6.4% and 6.5–6.9% groups (Table 3).

After adjustment for HbA_{1c} levels, the duration of hypoglycemia with glucose values of <70 mg/dL was significantly shorter in patients taking incretin-related agents (DPP-4 inhibitors or GLP-1 receptor agonists) than in those not taking these drugs (2.3 vs 3.8 min/h, $P < 0.05$). When DPP-4 inhibitors and GLP-1 receptor agonists were analyzed independently, no significant reduction of the duration of hypoglycemia with these drugs was observed. There were no significant differences in the duration of hypoglycemia between patients taking or not taking other concomitant antidiabetic medications (Table 4).

No episodes of severe hypoglycemia were reported by the study patients. Unrecognized hypoglycemia (glucose of <70 mg/dL without a self-report of hypoglycemia) occurred in all patients for whom a glucose value of <70 mg/dL was recorded at least once ($n = 205$, 76%). A total of 18 of these patients also reported hypoglycemia with symptoms.

The wearing time for the sensor was 13.4 ± 1.5 days (mean ± SD). A total of 228 (85%) patients reported no pain or almost no pain during sensor insertion, and 240 (89%) patients reported no itching or almost no itching during sensor wear.

DISCUSSION

By CGM analysis with a large number of participants, we have shown here that the duration of hypoglycemia was inversely

Table 2 | Duration of hypoglycemia according to age, duration of diabetes, estimated glomerular filtration rate, body mass index, sulfonylurea dose or diabetic complications

	Duration (min/h)	Duration (min/h)	*P*
Hypoglycemia of <54 mg/dL			
Age (years)	<75	≥75	
	0.45 (*n* = 178)	0.81 (*n* = 91)	0.11
Duration of diabetes (years)	<15	≥15	
	0.29 (*n* = 111)	0.80 (*n* = 151)	<0.05
eGFR (mL/min/1.73 m^2)	<60	≥60	
	0.64 (*n* = 94)	0.55 (*n* = 171)	0.68
BMI (kg/m^2)	<25	≥25	
	0.65 (*n* = 68)	0.45 (*n* = 199)	0.38
Gliclazide (mg/day)	≤20	>20	
	0.23 (*n* = 58)	0.84 (*n* = 27)	<0.05
Glimepiride (mg/day)	≤1	>1	
	0.42 (*n* = 130)	1.5 (*n* = 38)	<0.01
	(+)	(–)	
Diabetic retinopathy	0.78 (*n* = 88)	0.48 (*n* = 173)	0.18
Diabetic nephropathy	0.50 (*n* = 103)	0.61 (*n* = 66)	0.58
Diabetic neuropathy	0.81 (*n* = 102)	0.42 (*n* = 167)	0.07
Macrovascular complications	0.57 (*n* = 69)	0.54 (*n* = 200)	0.89
Hypoglycemia of <70 mg/dL			
Age (years)	<75	≥75	
	2.2 (*n* = 178)	3.0 (*n* = 91)	0.09
Duration of diabetes (years)	<15	≥15	
	1.7 (*n* = 111)	3.0 (*n* = 151)	<0.01
eGFR (mL/min/1.73 m^2)	<60	≥60	
	3.1 (*n* = 94)	2.1 (*n* = 171)	0.06
BMI (kg/m^2)	<25	≥25	
	2.6 (*n* = 68)	2.2 (*n* = 199)	0.32
Gliclazide (mg/day)	≤20	>20	
	1.6 (*n* = 58)	4.2 (*n* = 27)	<0.01
Glimepiride (mg/day)	≤1	>1	
	1.8 (*n* = 130)	4.2 (*n* = 38)	<0.01
	(+)	(–)	
Diabetic retinopathy	2.9 (*n* = 88)	2.3 (*n* = 173)	0.26
Diabetic nephropathy	2.8 (*n* = 103)	2.2 (*n* = 166)	0.26
Diabetic neuropathy	2.9 (*n* = 102)	2.2 (*n* = 167)	0.12
Macrovascular complications	2.5 (*n* = 69)	2.4 (*n* = 200)	0.74

Data are adjusted by glycated hemoglobin level. $P < 0.05$ was considered significant. BMI, body mass index; eGFR, estimated glomerular filtration rate.
[Correction added on 2 October, after first online publication: Some alignments in the table have been amended.]

Table 3 | Mean glucose levels and other glycemic parameters according to glycated hemoglobin level

Parameter	≤6.4%	6.5–6.9%	7.0–7.4%	7.5–7.9%	≥8.0%
Mean glucose level (mg/dL)	118.3 ± 18.9*	134.0 ± 16.9*	144.4 ± 17.1*	155.7 ± 30.0*	179.4 ± 29.2
Duration of hyperglycemia (min/h)	5.5 ± 5.5*	9.7 ± 6.4*	13.3 ± 7.0*	17.5 ± 12.1*	27.6 ± 12.1
Duration of euglycemia (min/h)	47.7 ± 6.4*	47.7 ± 7.1*	44.9 ± 7.2*	40.9 ± 11.4*	31.9 ± 11.8
SD (mg/dL)	38.2 ± 8.4*	42.6 ± 10.7*	43.2 ± 10.5	46.1 ± 9.9	51.0 ± 13.1
MAGE (mg/dL)	95.8 ± 23.6*	107.6 ± 30.4*	110.3 ± 25.7	118.8 ± 26.8	123.6 ± 36.8
CV (%)	32.7 ± 7.2*	31.9 ± 7.2*	30.3 ± 7.6	30.0 ± 6.0	28.6 ± 6.7

Data are mean ± standard deviation (SD). *$P < 0.0125$ versus glycated hemoglobin level of ≥8.0% (unpaired Student's *t*-test). CV, coefficient of variation; MAGE, mean amplitude of glycemic excursions.

Table 4 | Duration of hypoglycemia according to concomitant antidiabetic medications

	Duration (min/h) (+)	Duration (min/h) (–)	*P*
Hypoglycemia of <54 mg/dL			
Incretin-related agents (DPP-4 inhibitors or GLP-1 receptor agonists)†	0.54 (*n* = 241)	0.82 (*n* = 28)	0.42
DPP-4 inhibitors	0.55 (*n* = 224)	0.67 (*n* = 45)	0.67
GLP-1 receptor agonists	0.40 (*n* = 18)	0.58 (*n* = 251)	0.66
Biguanides	0.63 (*n* = 183)	0.43 (*n* = 86)	0.38
Thiazolidinediones	0.44 (n = 40)	0.59 (*n* = 229)	0.60
SGLT-2 inhibitors	0.37 (*n* = 36)	0.6 (n = 233)	0.47
Alpha-glucosidase inhibitors	0.41 (*n* = 78)	0.63 (*n* = 191)	0.33
Hypoglycemia of <70 mg/dL			
Incretin-related agents (DPP-4 inhibitors or GLP-1 receptor agonists)†	2.3 (*n* = 241)	3.8 (*n* = 28)	<0.05
DPP-4 inhibitors	2.3 (*n* = 224)	3.2 (*n* = 45)	0.15
GLP-1 receptor agonists	2.1 (*n* = 18)	2.5 (*n* = 251)	0.69
Biguanides	2.7 (*n* = 183)	1.9 (*n* = 86)	0.13
Thiazolidinediones	2.6 (*n* = 40)	2.4 (*n* = 229)	0.85
SGLT-2 inhibitors	2.3 (*n* = 36)	2.5 (*n* = 233)	0.77
Alpha-glucosidase inhibitors	1.8 (*n* = 78)	2.7 (*n* = 191)	0.07

Data are adjusted by glycated hemoglobin level. †One participant administered both a dipeptidyl peptidase-4 (DPP-4) inhibitor and a glucagon-like peptide-1 (GLP-1) receptor agonist. SGLT-2, sodium–glucose cotransporter 2

correlated with HbA_{1c} level in patients with type 2 diabetes treated with sulfonylureas. Whereas previous CGM-based studies with smaller numbers of participants showed that hypoglycemia occurs more frequently in individuals treated with sulfonylureas than in those not taking these drugs, the relationship between HbA_{1c} level and the duration of hypoglycemia was not analyzed in these studies[4,16]. A meta-analysis found that the incidence of hypoglycemia was inversely correlated with baseline HbA_{1c} level in type 2 diabetes patients who initiated medications, including sulfonylureas, with the development of hypoglycemia being detected by symptoms or self-monitoring of blood glucose[17], which does not allow quantitative assessment. A CGM-based study with 101 type 1 diabetes patients treated with basal–bolus insulin therapy showed that the HbA_{1c} level was inversely correlated with the duration of hypoglycemia[18]. The present study is thus the first to investigate the relationship between HbA_{1c} level and the duration of hypoglycemia, as determined by CGM in type 2 diabetes patients treated with sulfonylureas.

Previous studies with CGM showed that hypoglycemia occurred more frequently during the night than during the daytime in insulin-treated patients with type 1 or type 2 diabetes[18,19]. In contrast, daytime hypoglycemic events were more frequent than nocturnal hypoglycemic events in a study based on self-reporting of such events[20]. In the present study, we found that the duration of nocturnal hypoglycemia was longer than that of daytime hypoglycemia, and became longer as the HbA_{1c} level decreased. A meta-analysis in insulin-treated patients with type 2 diabetes also showed that the incidence of nocturnal hypoglycemia was inversely correlated with HbA_{1c} level[21]. The 24-h glucose profiles of patients in the present study showed that glucose levels were lowest in the early hours of the morning irrespective of HbA_{1c} level. Of note, patients were not aware of most nocturnal hypoglycemic events, suggesting that healthcare providers should pay careful attention to night-time hypoglycemia, particularly in the early hours of the morning, in patients treated with sulfonylureas.

We found that diabetes duration, but not age, was directly related to the duration of hypoglycemia in patients treated with sulfonylureas. The duration of diabetes and age have previously been shown to be associated with the incidence of hypoglycemia in patients with type 2 diabetes in other treatment settings[21–23]. Furthermore, we found that the dose of sulfonylureas was associated with the duration of hypoglycemia. A study in which hypoglycemia was detected on the basis of a questionnaire administered to patients showed a weak positive association between sulfonylurea dose and hypoglycemia[24]. Treatment with DPP-4 inhibitors or with GLP-1 receptor agonists is associated with a reduced risk of self-reported hypoglycemia[25]. We have now shown that the duration of hypoglycemia with glucose values of <70 mg/dL was shorter for patients taking these drugs. Impairment of renal function (eGFR of <60 mL/min/m^2) tended to be related to the duration of hypoglycemia in the present study, with such impairment having previously been associated with an increased rate of severe hypoglycemic events in sulfonylurea-treated patients with type 2 diabetes[26].

The strengths of the present study include its multicenter design and large number of participants. Furthermore, CGM analysis allowed us to quantitatively evaluate the duration, timing and severity of hypoglycemia, and the study with outpatients was informative not only of hypoglycemia, but also of glycemic variability in a real-world setting. Here, we showed that that patients with an HbA_{1c} level of ≤6.4% were exposed

to glucose values of <70 mg/dL for >10% of the time during daily life (6.8 ± 5.6 min/h).

There were several limitations in the current study. First, the accuracy of the CGM device (FreeStyle Libre Pro) has not been fully characterized. The mean absolute relative difference of the device was reported to be 11.1%, which is not inferior to that of other conventional calibrated CGM devices[8]. Second, we did not collect information that might affect the duration of hypoglycemia, such as dietary and exercise habit, alcohol intake or socioeconomic status. Third, given that the present study was carried out at diabetes units of core hospitals of the community, it is unknown whether the current results are applicable to general patients cared for by general practitioners. Finally, whereas we recruited 300 patients, which is our predetermined sample size, we could only analyze the data of 269 patients because of the loss and the inappropriate length (<7 days) of available data. The sample size of 269 is, however, larger than the required number of patients with the statistical power of 75% (250).

We have shown for the first time that the duration of hypoglycemia was inversely correlated with HbA_{1c} level in patients with type 2 diabetes treated with sulfonylureas. Healthcare providers, as well as patients themselves, should thus pay careful attention to the possibility of hypoglycemia development during treatment with sulfonylureas.

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DISCLOSURE

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