https://doi.org/10.4082/kjfm.18.0051 • Korean J Fam Med 2019;40:212-219

KJFM
Korean Journal of Family Medicine

eISSN: 2092-6715

■ Original Article

Frequency and Severity of Hypoglycemia in Type 2 Diabetes Mellitus Patients Treated with a Sulfonylurea-Based Regimen at University-Affiliated Hospitals in Korea: The Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects Study

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Background: We assessed the frequency and severity of hypoglycemia in type 2 diabetes mellitus patients treated with sulfonylurea monotherapy or sulfonylurea+metformin.

Methods: We conducted a retrospective, observational, cross-sectional study in 2011 and 2012 including patients with type 2 diabetes mellitus aged ≥30 years who were treated with ≥6 months of sulfonylurea monotherapy or sulfonylurea+metformin at 20 university-affiliated hospitals in Korea. At enrollment, glycated hemoglobin (HbA1c) was assessed; participants completed self-reported questionnaires describing hypoglycemia incidents over the past 6 months. A review of medical records up to 12 months before enrollment provided data on demographics, disease history, comorbidities, laboratory results, and drug usage.

Received: March 29, 2017, Revised: August 10, 2018, Accepted: September 10, 2018
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Results: Of 726 enrolled patients, 719 were included (55.6% male); 31.7% and 68.3% were on sulfonylurea monotherapy and sulfonylurea+metformin, respectively. Mean±standard deviation age was 65.9±10.0 years; mean HbA1c level was 7.0%±1.0%; 77.8% of patients had hypertension (89.4% used antihypertensive medication); 60.5% had lipid disorders (72.5% used lipid-lowering medication); and 52.0% had one or more micro- or macrovascular diseases. Among patients with A1c measurement (n=717), 56.4% achieved therapeutic goals (HbA1c <7.0%); 42.4% (305/719) experienced hypoglycemia within 6 months of enrollment; and 38.8%, 12.9%, 12.7%, and 3.9% of patients experienced mild, moderate, severe, and very severe hypoglycemia symptoms, respectively. Several reported hypoglycemia frequency as 1–2 times over the last 6 months. The mean number of very severe hypoglycemia episodes was 3.5±5.5.
Conclusion: Among type 2 diabetes mellitus patients treated with sulfonylurea-based regimens, glycemic levels were relatively well controlled but hypoglycemia remained a prevalent side effect.

Keywords: Glycated Hemoglobin A; Hypoglycemia; Sulfonylurea; Type 2 Diabetes Mellitus; Metformin

INTRODUCTION

Diabetes is a global health issue estimated to have affected 336 million people worldwide in 2011. Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of all diagnosed diabetes cases. The Western Pacific region contributes the greatest number of global cases, where approximately 132 million people are living with the disease. The prevalence of diabetes in this region is expected to increase from 8.5% in 2011 to 10.6% by 2030.[1] Recently urbanized and affluent populations from the more prosperous areas of the Western Pacific region are under particular threat. In Korea, the prevalence of diabetes is higher than the regional average, affecting 8.9% of the population.[1]

To slow T2DM progression and help patients reach glycemic targets, expert guidelines stress the importance of comprehensive disease management. Combined with lifestyle modification, several oral antihyperglycemic agents are recommended to help patients achieve glycemic targets. Sulfonylureas (SUs) are some of the most widely used oral antihyperglycemic agents worldwide and have been the predominant treatment in Korea as monotherapy and also as dual therapy with metformin. SUs act on the beta cells to stimulate insulin secretion; however, they do so without regard to blood glucose levels, and therefore can cause a rapid decrease in glucose levels. Given this mechanism, hypoglycemia, defined as abnormally low plasma glucose, is a common side effect of SU-based therapy. This is especially the case among patients with renal failure and compromised kidney function, as SUs are excreted by the kidneys and may accumulate in these patients.[2,3] Patients treated with SUs have also been found to have a higher risk of adverse cardiovascular outcomes and mortality compared with patients who are treated with monotherapy metformin.[4,5]

The association between SUs and hypoglycemia is of particular concern because hypoglycemia causes significant physical and psychosocial morbidity and is considered as the most limiting factor in glycemic management.[6] Therefore, understanding the risk factors associated with hypoglycemia is imperative to improving glycemic control in patients with T2DM. Previous studies have found that the risks of hypoglycemia include behavioral, therapeutic, and physiologic factors.[6-10]

Given the dominant use of SU-based therapy in Korea and its association with hypoglycemia, it is important to understand treatment patterns and the incidence of hypoglycemia in Korea specifically. According to UBIquitous STatistics data from 2009, non-endocrinology physicians prescribed more than half of all diabetes treatments in Korea.[11] For patients treated with SUs in these settings, pre-existing cardiovascular or kidney disease, treatment patterns, glycated hemoglobin (HbA1c) goal attainment rates, and diabetes complication rates remain unknown. The prevalence and severity of hypoglycemia, and its impact on patient satisfaction and quality of life (QoL), also remain unknown.

To address this gap in knowledge, the objective of this study was to assess the frequency and severity of hypoglycemia in SU-treated patients in Korea, as well as factors associated with hypoglycemia, and its impact on patient satisfaction and QoL among patients with T2DM treated with SU in cardiology, nephrology, and family practice settings in Korea. Further, we assessed goal attainment rates, treatment patterns, and incidence of diabetes complications.

METHODS

1. Study Design

The Naturalistic Evaluation of Hypoglycemic Events in Diabetic Study (NEEDS) was a multicenter, observational study using both retrospective and cross-sectional data from a cohort of consecutively selected patients with T2DM of 10 hospitals in Seoul and 10 hospitals from other provinces; 19 were university-affiliated hospitals and one was a secondary general hospital in university-affiliated hospitals in Korea. Patients were selected from cardiology, nephrology, and family practice settings only. The study population included adults diagnosed with T2DM according to American Diabetes Association (ADA) criteria, who were 30 years of age or older and had been treated with SU monotherapy or SU plus metformin combination therapy for at least 6 months by a cardiologist, nephrologist, or family practitioner. In the Asia Pacific Real-Life Effectiveness and Care Patterns of Diabetes Management (Asia Pacific RECAP-DM) Study, the prevalence of hypoglycemia was reported at 36% (95% confidence interval, 33.8% to 37.8%). Assuming a proportion of 0.36, a confidence level of 0.95, and a desired

https://doi.org/10.4082/kjfm.18.0051

margin of error of ±3.5%, 723 patients were required for this study. Potential patients were screened during a 6-month period from May 2011 to June 2012, and eligible patients were enrolled in the study at their usual physician office visits, after signing an informed consent form. If included, the patient's medical records were reviewed at enrollment and retrospectively over the 12 months preceding enrollment. Patients who signed the informed consent form were enrolled and a cross-sectional survey of patients was also conducted. The institutional review board approval for the study was not required because of the nature of the study. And this study was conducted in compliance with the standards of the Declaration of Helsinki and current ethical guidelines.

2. Study Sample

Patients included in the study were diagnosed with T2DM using criteria of the ADA[12] and were at least 30 years of age at the time of diagnosis. Patients must have received outpatient diabetes care from a cardiologist, nephrologist, or family practitioner, and must have been treated with SU monotherapy or SU plus metformin combination therapy for at least 6 months prior to enrollment.

Patients were excluded from the study sample if they were pregnant, diagnosed with type 1 or gestational DM, or had received any antidiabetic treatment from an endocrinologist/diabetologist within 6 months of the enrollment date. Also excluded from the study were patients who received any oral antihyperglycemic agent other than SU or SU plus metformin, or those who required daily concomitant usage of insulin. Of note, patients who received rapid acting insulin during hospitalization, an emergency room visit, kidney dialysis, or an invasive procedure in an outpatient department were retained in the study sample.

3. Outcome Measures

Patient characteristics were extracted from medical chart reviews at enrollment and for the 12 months preceding enrollment, and also collected using a cross-sectional patient survey. At enrollment, all participating patients received a standard blood test after an overnight fast. Clinical outcomes measured in the study included HbA1c, fasting plasma glucose, serum creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and urinary albumin levels. A target HbA1c level of less than 7.0% was applied, as recommended by the ADA. In addition, each patient's body weight, blood pressure, and waist circumference were measured, and information on alcohol and tobacco use, dietary management, and family history was also collected.

The main outcome variables of the study were the incidence and severity of hypoglycemia. Patients were asked if they had experienced symptoms of hypoglycemia in the 6 months prior to study enrollment, based on a list of symptoms provided (sweating, confusion/feeling disoriented, shakiness, clumsy or jerky movements, dizziness, sudden moodiness or behavior changes, hunger, tingling sensations around the mouth, difficulty concentrating, headache, and pale skin color). Patients who recorded a positive response were further asked to rate the severity of their episodes as mild (little or no interruption of activities, and did not feel the need for assistance to manage symptoms), moderate (some interruption of activities, but did not feel the need for assistance to manage symptoms), severe (felt the need for assistance from others to manage symptoms), or very severe (needed medical attention). Patients who experienced hypoglycemia also reported the intensity of events by describing how 'bothered' they were by their hypoglycemia symptoms, which ranged in intensity from 'not concerned' to 'extremely bothered.'

Patient satisfaction with treatment was measured using the Treat-

Table 1. Patient characteristics and laboratory values at enrollment (N=719)

Characteristic	Value
Clinical setting	
Cardiology	417 (58.0)
Nephrology	162 (22.5)
Family medicine	142 (19.8)
Male	400 (55.6)
Age (y)	65.9±10.0
Body mass index (kg/m^2)	25.8±3.3
Waist circumference (cm)	91.0±8.7
Tobacco use	
Never	376 (52.3)
Former (quit >1 mo)	217 (30.2)
Current	95 (13.2)
Unknown	31 (4.3)
Alcohol use	
Never	379 (52.7)
Occasionally/on weekends	201 (28.0)
Daily	25 (3.5)
Unknown	114 (15.9)
Diet	
Low sugar	270 (37.7)
Low caloric intake	286 (39.8)
Family history	
Family history of macrovascular conditions*	71 (9.9)
Family history of diabetes	206 (28.7)
Parental history of diabetes (N=715)	167 (23.4)
Type 2 diabetes mellitus history	
Duration of type 2 diabetes mellitus (y)	8.6±6.7
Age at diagnosis (y)	57.3±10.1
Self-monitoring of blood glucose	319 (44.4)
Laboratory values	
Glycated hemoglobin (%)	7.0±1.0
Fasting plasma glucose (mg/dL)	129.1±41.8
Total cholesterol (mg/dL)	157.4±32.9
Low-density lipoprotein cholesterol (mg/dL)	87.7±27.4
High-density lipoprotein cholesterol (mg/dL)	46.2±10.8
Triglycerides (mg/dL)	149.8±80.1
Serum creatinine (mg/dL)	1.2±1.2
eGFR/MDRS	78.2±49.2
Urinary albumin excretion (mL/min/1.73 mg/g)	113.8±424.1

Values are presented as number (%) or mean±standard deviation. Mean and standard deviation based on patients with no missing values.
*History of macrovascular conditions refers to history of myocardial infarction or stroke.
Estimated glomerular filtration rate with Modification of Diet in Renal Disease (mL/min/1.73 m^2)

ment Satisfaction Questionnaire for Medication, which assesses patient perceptions of the treatment's effectiveness, side effects, and convenience. Patients' health-related QoL was assessed using two generic measures of health status, the EuroQol Visual Analog Scale (EQ-VAS) and the EuroQol-5 dimensions (EQ-5D) questionnaire. The EQ-VAS measures a patient's self-reported health on a scale from 0 (worst health state) to 100 (best health state), and the EQ-5D describes five domains of QoL (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Finally, the Hypoglycemia Fear Survey-II was used to quantify levels of worry and fear among patients, and comprises 18 questions that measure the degree of patient fear in the past 6 months, scaled from 0 to 72 with higher scores indicating greater worry and fear.

4. Statistical Analysis

We performed descriptive analysis to assess demographics, disease characteristics, clinical outcomes, treatment patterns, and the frequency and severity of hypoglycemia. To investigate factors associated with hypoglycemia, differences in patient demographics, disease characteristics, and clinical outcomes were assessed in patients with hypoglycemia versus patients without hypoglycemia using t-tests for continuous variables or χ^2 tests for categorical variables. To describe the broader impact of hypoglycemia, a comparison of patient satisfaction, QoL, and levels of worry and fear was also conducted in patients who experienced hypoglycemia versus those who did not. Multivariable logistic regression analysis was also used to explore key factors associated with hypoglycemia. Statistical significance was evaluated at a 5% significance level throughout the study.

RESULTS

In total, we enrolled 726 patients in this study, of which 419 patients were treated in cardiology, 162 in nephrology, and 145 in family medicine settings. Seven patients failed to meet all the inclusion criteria and were excluded from the sample, which left 719 patients in the final sample.

1. Patient Characteristics

Patient characteristics are summarized in Table 1. The average age of patients (mean±standard deviation) was 65.9±10.0 years, and 55.6% of patients were male. Average body mass index (BMI) was 25.8±3.3 kg/m^2, and mean waist circumference was 91.0±8.7 cm. Mean duration of T2DM was 8.6±6.7 years, and average age at diagnosis was 57.3±10.1 years. The average HbA1c level at study enrollment was 7.0%±1.0%, and mean fasting plasma glucose was 129.1±41.8 mg/dL. The percentage of patients with a family history of T2DM among first-degree relatives was 23.4%, and 44.4% regularly self-monitored their blood glucose.

2. Glycated Hemoglobin Goal Attainment and Treatment Patterns

Table 2 explores treatment patterns, HbA1c goal attainment, and comorbidities among study participants. A total 31.7% of patients were

Table 2. Treatment pattern, HbA1c goal attainment rate, and comorbidities (N=719)

Variable	Value
Treatment pattern	
SU monotherapy	228 (31.7)
SU+metformin combination therapy	491 (68.3)
HbA1c at goal*	
HbA1c <7.0%	404 (56.4)
HbA1c <6.5%	224 (31.2)
Concomitant medications	
Antihypertensive medications	643 (89.4)
Lipid-lowering medications	521 (72.5)
Weight-reducing medications	1 (0.1)
Major medical events (>10%)	
Hypertension	559 (77.8)
Lipid disorder	435 (60.5)
Ischemic heart disease	208 (28.9)
Renal failure, kidney disease	86 (12.0)
Macro-/microvascular conditions†,‡	
Macro- or microvascular conditions†,‡	374 (52.0)
Macrovascular conditions†	304 (42.3)
Microvascular conditions‡	86 (12.0)

Values are presented as number (%).
HbA1c, glycated hemoglobin; SU, sulfonylurea.
*HbA1c goal attainment rate calculated in 717 patients. †Macrovascular conditions refer to ischemic heart disease, congestive heart failure, myocardial infarction, stroke, atrial fibrillation, and peripheral vascular disease. ‡Microvascular conditions refer to blindness, amputation, and renal failure.

Table 3. Frequency and severity of hypoglycemia (N=719)

Variable	Value
Hypoglycemia in the last 6 months	305 (42.4)
Hypoglycemia experience and severity (combined)*	
Mild	279 (38.8)
Moderate	93 (12.9)
Severe	91 (12.7)
Very severe	28 (3.9)
Hypoglycemia experience and maximum severity*	
Mild	183 (25.5)
Moderate	28 (3.9)
Severe	66 (9.2)
Very severe	28 (3.9)
Intensity of hypoglycemia symptoms† (respondents, n=282)	
Not at all concerned	77 (27.3)
Not bothered	69 (24.5)
A little bit bothered	95 (33.7)
Somewhat bothered	22 (7.8)
Very bothered	14 (5.0)
Extremely bothered	5 (1.8)

Values are presented as number (%).
*Hypoglycemia severity was categorized as (1) mild (little or no interruption of activities and no assistance needed to manage symptoms); (2) moderate (some interruption of activities and no assistance needed to manage symptoms); (3) severe (needed assistance of others to manage symptoms); and (4) very severe (episodes that required medical assistance). †The intensity of hypoglycemia symptoms within 6 months prior to enrollment was rated subjectively by patients based on their perception.

https://doi.org/10.4082/kjfm.18.0051

treated with SU monotherapy, and 68.3% were on SU plus metformin combination therapy. At enrollment, 56.4% of patients had achieved an HbA1c below 7.0%, and 31.2% of patients had an HbA1c below 6.5%.

Over the 12-month medical chart review period, 77.8% of patients had hypertension and 89.4% used antihypertensive medication. Moreover, 60.5% of patients had lipid disorders and 72.5% used lipid-lowering medications; 52.0% of patients had one or more macro- or microvascular diseases.

3. Hypoglycemia and Associated Factors

Table 3 explores the frequency and severity of hypoglycemia in the study participants. In total, 42.4% of patients had experienced hypoglycemia symptoms at least once in the 6 months prior to enrollment.

Table 4. Clinical factors associated with hypoglycemia

Variable	With hypoglycemia (N=305)	Without hypoglycemia (N=414)	P-value
Male	166 (54.4)	234 (56.5)	0.5762
Age (y)	65.2±10.2	66.4±9.8	0.1108
Body mass index (kg/m^2)	25.7±3.2	25.8±3.3	0.5866
Waist circumference (cm)	90.7±8.9	91.2±8.6	0.4128
Tobacco use			0.6333
Never	154 (50.5)	222 (53.6)	
Former (quit >1 mo)	92 (30.2)	125 (30.2)	
Current	43 (14.1)	52 (12.6)	
Unknown	16 (5.3)	15 (3.6)	
Alcohol use			0.7902
Never	159 (52.1)	220 (53.1)	
Occasionally/on weekends	82 (26.9)	119 (28.7)	
Daily	12 (3.9)	13 (3.1)	
Unknown	52 (17.1)	62 (15.0)	
Diet			
Low sugar*	121 (39.8)	149 (36.1)	0.3090
Low caloric intake	128 (42.1)*	158 (38.2)	0.2865
Family history			
Family history of macrovascular conditions	41 (13.4)	30 (7.3)	0.0215
Family history of diabetes	111 (36.4)	95 (23.0)	0.0004
Parental history of diabetes	88 (28.9)	79 (19.3)†	0.0027
T2DM history			
Duration of T2DM (y)	8.7±6.4	8.6±6.8	0.8206
Age at diagnosis (y)	56.5±10.0	57.9±10.2	0.0806
Self-monitoring of blood glucose	149 (48.9)	170 (41.1)	0.0377
HbA1c at goal			
HbA1c <7.0%	170 (55.7)	234 (56.8)†	0.7775
HbA1c <6.5%	91 (29.8)	133 (32.3)†	0.4849
Concomitant medications			
Antihypertensive medications	281 (92.1)	362 (87.4)	0.0432
Lipid-lowering medications	244 (80.0)	277 (66.9)	0.0001
Weight-reducing medications	1 (0.3)	0	0.6688
eGFR with Modification of Diet in Renal Disease			0.4968
No. of patients	305	414	
eGFR (mL/min/1.73 m^2)	79.8±67.5	77.0±29.1	
Stage 1: eGFR ≥90 mL/min/1.73 m^2	86 (28.3)	129 (31.2)	
Stage 2: eGFR 60–89 mL/min/1.73 m^2	135 (44.4)	171 (41.4)	
Stage 3: eGFR 30–59 mL/min/1.73 m^2	71 (23.4)	90 (21.8)	
Stage 4: eGFR 15–29 mL/min/1.73 m^2	5 (1.6)	17 (4.1)	
Stage 5: eGFR <15 mL/min/1.73 m^2	7 (2.3)	6 (1.5)	
Macro-/microvascular conditions‡,§			
Macro- or microvascular conditions‡,§	174 (57.1)	200 (48.3)	0.0204
Macrovascular conditions*	148 (48.5)	156 (37.7)	0.0036
Microvascular conditions†	32 (10.5)	54 (13.0)	0.2974

Values are presented as number (%) or mean±standard deviation. Mean±standard deviation based on patients with no missing values.
T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate.
*For low sugar and low caloric intake, this was calculated out of 304 patients with hypoglycemia and 413 without. †The total number of patients was 410. ‡Macrovascular conditions refer to ischemic heart disease, congestive heart failure, myocardial infarction, stroke, atrial fibrillation, and peripheral vascular disease. §Microvascular conditions refer to blindness, amputation, and renal failure.

The most commonly reported frequency of hypoglycemia per patient was once or twice in that period. On average, patients who ever reported very severe hypoglycemia experienced hypoglycemia 3.5 times over the 6 months prior to enrollment, and the number of events in this subgroup ranged from 1 to 30 times in that period.

Assessing the self-reported severity of patients' worst hypoglycemia event, 38.8% of patients reported their worst hypoglycemia symptoms as mild, 12.9% as moderate, 12.7% as severe, and 3.9% as very severe. Based on responses from the 282 patients who experienced hypoglycemia, 95 (33.7%) were slightly bothered by their hypoglycemia symptoms, 22 (7.8%) were somewhat bothered, 14 (5.0%) were very bothered, and five (1.8%) were extremely bothered by their symptoms.

Table 4 compares patients who experienced hypoglycemia with those who did not, to assess demographic and clinical factors associated with hypoglycemia events. A significantly larger proportion of patients with hypoglycemia had comorbid macrovascular diseases (including ischemic heart disease, congestive heart failure, myocardial infarction, atrial fibrillation, peripheral vascular disease, and stroke), as compared with patients who did not have hypoglycemia (48.5% versus 37.7%, P=0.0036). In comparison with their counterparts without hypoglycemia, a greater proportion of patients who experienced hypoglycemia also reported a family history of macrovascular disease (13.4% versus 7.3%, P=0.0215), a family history of diabetes (36.4% versus 23%, P=0.0004), and that they self-monitored their blood glucose (48.9% versus 41.1%, P=0.0377). Likewise, a higher proportion of patients with hypoglycemia concomitantly used antihypertensive medications (92.1% versus 87.4%, P=0.0432) and lipid-lowering medications (80.0% versus 66.9%, P=0.0001) than those without hypoglycemia. There were no significant differences between the two groups when comparing age, sex, use of tobacco and alcohol, dietary management, duration of T2DM, baseline estimated glomerular filtration rate, or BMI.

Table 5 compares treatment satisfaction, QoL, and levels of worry and fear between patients who experienced hypoglycemia and those who did not. On average, patients with hypoglycemia were less satisfied with their treatment's effectiveness (63.1 versus 65.5, P=0.0169), side effects (95.3 versus 98.6, P<0.0001), and convenience (66.3 versus 68.7, P=0.0180) than their counterparts. Patients with hypoglycemia also reported, on average, lower QoL (EQ-5D time trade-off: 0.87 versus 0.90, P=0.0029) and higher levels of worry about hypoglycemia

Table 5. Impact of hypoglycemia

Variable	With hypoglycemia (N=305)	Without hypoglycemia (N=414)	P-value
Treatment satisfaction			
Effectiveness	63.1±13.1	65.5±12.8	0.0169
Side effects	95.3±14.0	98.6±6.9	<0.0001
Convenience	66.3±13.9	68.7±12.9	0.0180
Global satisfaction	62.5±14.2	63.5±14.6	0.3762
EQ-5D			
Mobility			0.0139
I have no problems with walking	195 (64.14)	299 (72.93)	
I have some problems with walking	108 (35.53)	107 (26.10)	
I am confined to bed	1 (0.33)	4 (0.98)	
Self-care			0.1034
I have no problems with self-care	276 (90.79)	377 (91.95)	
I have some problems washing or dressing myself	27 (8.88)	26 (6.34)	
I am unable to wash or dress myself	1 (0.33)	7 (1.71)	
Usual activities			0.0053
I have no problems with performing my usual activities	228 (75.00)	345 (84.15)	
I have some problems with performing my usual activities	73 (24.01)	60 (14.63)	
I am unable to perform my usual activities	3 (0.99)	5 (1.22)	
Pain/discomfort			0.0400
I have no pain or discomfort	175 (57.57)	274 (66.83)	
I have moderate pain or discomfort	116 (38.16)	123 (30.00)	
I have extreme pain or discomfort	13 (4.28)	13 (3.17)	
Anxiety/depression			<0.0001
I am not anxious or depressed	190 (62.50)	317 (77.32)	
I am moderately anxious or depressed	105 (34.54)	89 (21.71)	
I am extremely anxious or depressed	9 (2.96)	4 (0.98)	
EQ-5D time trade-off	0.9±0.1	0.9±0.1	0.0029
EQ-Visual Analog Scale	70.2±16.7	73.5±16.5	0.0074
Worry scale of Hypoglycemia Fear Survey-II			
Total	9.39±13.1	5.2±9.3	<0.0001

Values are presented as mean±standard deviation or number (%). Mean and standard deviation based on patients with no missing values.
EQ-5D, EuroQol-5 dimensions.

https://doi.org/10.4082/kjfm.18.0051

(9.39 versus 5.21, P<0.0001) than patients without hypoglycemia.

DISCUSSION

The objective of the NEEDS was to assess the incidence and severity of hypoglycemia, as well as goal attainment rates and treatment patterns among patients with T2DM treated with SU in cardiology, nephrology, and family practice settings at university-affiliated hospitals in Korea. Results from this study indicated that glycemic levels among patients with T2DM treated with SU or SU plus metformin therapy in Korea were relatively well controlled. However, 42.4% of study participants had experienced at least one hypoglycemia symptom in the 6 months prior to enrollment. The incidence and severity of hypoglycemia symptoms observed in this study were comparable to those reported in Western countries.[13,14] Our results were also within range of those of a similar study conducted in Asia in 2007, the Asia Pacific RECAP-DM Study, which reported that 36% of patients with T2DM receiving oral antihyperglycemic agents experienced hypoglycemia symptoms within the 6 months preceding enrollment.[15] The higher rate of hypoglycemia reported in this study may be because all patients in the sample were treated with an SU-based regimen, of which hypoglycemia is a known side effect. The higher incidence of hypoglycemia reported here may also reflect unique challenges to diabetes management faced in cardiology, nephrology, and family practice settings, where familiarity with best practice in diabetes management may be less well known.

Another objective of this study was to assess factors related to hypoglycemia, and the impact of hypoglycemia on patient satisfaction and QoL. Results confirmed that among Korean patients with T2DM treated with SUs, patient-reported that hypoglycemia was associated with a significantly lower QoL, including greater anxiety and depression, more pain and discomfort, and greater difficulty performing routine daily activities. We also found that hypoglycemia was significantly associated with lower treatment satisfaction, including worse perceptions of the treatment's effectiveness, side effects, and convenience. As expected, self-reported hypoglycemia symptoms were also associated with greater fear of hypoglycemia. These results are again consistent with findings of the Asia Pacific RECAP-DM Study.[16]

These findings suggested that the QoL of patients with T2DM could be improved by educational interventions addressing a patient's worries about hypoglycemia. There is some evidence that training patients to recognize and avoid severe hypoglycemia episodes may reduce their fear of side effects.[16] Further, because a patient's fears about a therapy's side effects and its effectiveness mediate a physician's willingness to intensify therapy, reducing patients' fear may lead to therapy intensification and thus improve glycemic control.[17]

Results from this study were also consistent with previously published literature reporting that the presence of hypoglycemia was associated with the use of concomitant drug therapy aimed at reducing the risk of micro- and macrovascular complications, as well as decreased adherence to diet management and a reduction in patients' willingness to take medications as directed.[18] Those findings imply that antidiabetic therapy that has a lower risk of hypoglycemia may increase patient adherence and help patients achieve long-term benefits associated with well-controlled blood glucose levels.[19]

This study has several limitations. Outcomes measured at enrollment were cross-sectional, and therefore causality cannot be inferred. In particular, no conclusions on the change in glycemic control among patients over the treatment period could be ascertained. This study also relied on self-reported data, particularly the incidence, severity, and impact of hypoglycemia. If patients failed to recall all hypoglycemia events, then the measures of incidence and severity in this sample may be underestimated. However, patients who experienced hypoglycemia may have recalled their treatment experience with better accuracy than those who had no hypoglycemia events. Moreover, because patients with hypoglycemia are more likely to report negative outcomes than their counterparts, this may have exaggerated the differences between the two groups. Future studies with more rigorous designs are needed to further explore the incidence and impact of hypoglycemia on patients' well-being, adherence, and long-term clinical outcomes. Further, whereas the occurrence of hypoglycemia significantly reduced mean EQ-5D scores, it is not clear whether this result met the criteria for a minimal clinically important difference. Estimates of the minimal clinically important difference for the EQ-VAS range from 4.2 to 14.8[20] and from 3.8 to 8.4,[21] and the difference in this study was 3.38 (Table 5). Finally, because patients were only recruited from cardiology, nephrology, and family practice settings at university-affiliated hospitals in Korea, these results may not be generalizable to other practice areas or other regions.

A substantial proportion of patients with T2DM receiving SU-based regimens did not achieve optimal HbA1c control and experienced hypoglycemia during their recent treatment period. Patient-reported hypoglycemia symptoms were common in patients receiving SU-based treatment, and were associated with significantly lower treatment satisfaction and lower QoL, as well as greater worry about hypoglycemia. To improve glycemic control in patients with T2DM in Korea, it is important to educate patients and physicians on strategies to avoid hypoglycemia.

CONFLICT OF INTEREST

Wonju Jeung is an employee of MSD Korea. No potential conflict of interest relevant to this article was reported.

FUNDING

This study was funded by MSD Korea. Medical writing was provided by Zhiyi Li of Asclepius Analytics Ltd., with funding provided by MSD Korea, and editorial assistance was provided by Cactus Communications Pvt. Ltd., with funding provided by MSD Korea.

ACKNOWLEDGMENTS

The authors would like to thank all investigators for this study: Jin Ho Kang, Kangbuk Samsung Medical Center; Seung Ho Heo, Keimyung University Dongsan Medical Center; Ki Dong Yoo, St. Vincent's Hospital; Hui Kyung Jeon, Uijeongbu St. Mary's Hospital; Duk Hee Kang, Ewha Womans University Mokdong Hospital; Sang Ho Lee, Kyung Hee University Gangdong Hospital; Yong Lim Kim, Kyungpook National University Hospital; Jung Gyu Lee, Pusan National University Hospital; Byung-Wook Yoo, Soonchunhyang University Hospital; and Yong Gyun Roh, Hallym University Medical Center.

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https://doi.org/10.4082/kjfm.18.0051