


Factors associated with greater benefit of a national reimbursement policy for blood glucose test strips in adult patients with type 1 diabetes: A prospective cohort study

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Keywords

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ABSTRACT

Aims/Introduction: We aimed to identify factors independently associated with greater benefit of a national reimbursement policy for blood glucose test strips in adult patients with type 1 diabetes, in terms of glycemic control and the rate of severe hypoglycemia.

Materials and Methods: This was a prospective cohort study of 466 adult patients with type 1 diabetes from five tertiary referral hospitals who registered for a national reimbursement program for blood glucose strips and were then followed-up for 12 months. Factors associated with a > 5% reduction in glycated hemoglobin (HbA1c) and decreased rate of severe hypoglycemia (SH) at 12 months from baseline were evaluated.

Results: At the end of the 12 months of follow up, 158 of 466 patients (33.9%) achieved >5% reduction in HbA1c, and 47 of 111 patients (42.3%) had a decreased rate of SH relative to baseline. Higher HbA1c ($P < 0.001$), lower total daily insulin dose at baseline ($P = 0.048$) and an increase in self-monitoring of blood glucose (SMBG) frequency during follow up ($P = 0.001$) were independently associated with >5% reduction in HbA1c. A higher SMBG frequency ($P < 0.001$), higher rate of SH at baseline ($P = 0.029$) and lack of hypoglycemic unawareness ($P = 0.044$) were independently associated with an increase in the frequency of SMBG during follow up. Higher SMBG frequency at baseline ($P < 0.001$) was independently associated with a decreased rate of SH.

Conclusions: Several factors, including higher SMBG frequency at baseline, were independently associated with reduced HbA1c and a decreased rate of severe hypoglycemia, showing that patients with these characteristics derive the most benefit from reimbursement of blood glucose test strips.

INTRODUCTION

Self-monitoring of blood glucose (SMBG) is accepted as an integral part of self-management of diabetes in order to achieve

glycemic targets and prevent diabetes-related complications¹. SMBG helps patients to detect hypoglycemia and adjust their insulin doses appropriately, and more frequent SMBG is associated with better metabolic control for type 1² and type 2 diabetes being treated with insulin³. The Diabetes Control and Complication Trial provided evidence that intensive glycemic

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control facilitated by daily glucose monitoring (SMBG ≥ 4 times/day) in type 1 diabetes mellitus patients delayed the onset and slowed the progression of diabetes-related microvascular complications¹. Most clinical practice guidelines⁴⁻⁷ recommend carrying out SMBG for patients who are receiving insulin therapy, and frequent SMBG is recommended for patients receiving multiple-daily insulin or insulin pump therapy.

The presence of diabetes⁸ and diabetes-associated complications⁹ is associated with increased healthcare costs and decreased work productivity¹⁰. Diabetes-related healthcare costs are known to increase in accordance with higher glycated hemoglobin (HbA1c)¹¹, poor treatment adherence¹² and fewer applications of SMBG¹³. Even though tight glycemic control achieved through frequent SMBG can attenuate medical costs associated with treatment and long-term management of diabetes-associated complications¹⁴, the frequency of daily SMBG presumably decreases as out-of-pocket costs for blood glucose test strips increase¹⁵. In support of this, lack of insurance coverage for blood glucose test strips was found to be associated with poor glycemic control in Canadian patients with type 2 diabetes¹⁶.

Although the benefits of insurance coverage for the cost of SMBG are clear¹⁷⁻¹⁹, the rapidly increasing burden of national medical costs as a result of global aging and limited resources is becoming a great challenge in several countries. This motivated us to define the patient group who would most benefit from reimbursement for SMBG in order to enable prioritization of limited resources. The Korea National Health Insurance Service (KNHIS) recently instituted a policy to reimburse the cost of self-monitoring blood glucose test strips for use up to four times a day for patients with type 1 diabetes. Since the introduction of this policy in 2011, there has been a cumulative increase in the number of Korean patients with adult type 1 diabetes who have registered for the reimbursement program²⁰. The purpose of the present prospective cohort study was to identify factors independently associated with greater benefit of the national reimbursement policy for blood glucose test strips in adult patients with type 1 diabetes at 12 months after registration for the reimbursement program, in terms of glycemic control and rate of severe hypoglycemia.

METHODS

Study design

During the study period, the KNHIS program for the reimbursement of blood glucose test strips allowed all domestic doctors of internal medicine, pediatrics and family medicine to issue registration forms if their patients with type 1 diabetes mellitus met the criteria for enrollment. After registration, patients could obtain reimbursement for the cost of blood glucose test strips used up to four times per day. Eligibility for the reimbursement program was limited to those who required insulin treatment (mandatory) and met at least one of following criteria: (i) fasting C-peptide < 0.6 ng/mL; (ii) glucagon stimulated C-peptide < 1.8 ng/mL; (iii) positive for glutamic-acid-decarboxylase and/or other autoantibodies;

(iv) 24-h urine C-peptide level < 30 μ g per day; or (v) a history of diabetic ketoacidosis.

The same criteria were used as eligibility criteria for the present prospective cohort study, which recruited adult (age > 20 years) patients with type 1 diabetes treated at one of five university-affiliated tertiary referral hospitals (Samsung Seoul Hospital, Severance Hospital, Asan Medical Center, Seoul Catholic Hospital or Kangbuk Samsung Hospital in Seoul, Korea) between January 2011 and March 2015; these patients additionally consented to participate in this prospective cohort study, and to provide laboratory and anthropometric data and complete a questionnaire, which were not part of the national reimbursement policy. After the study, participants registered for the KNHIS reimbursement program at baseline, and biochemical data at 0, 6 and 12 months from baseline were obtained. The frequency of SMBG (times/day), and history or experience with severe hypoglycemia (times/month) at 0, 6 and 12 months from baseline were obtained through interviews to complete the comprehensive questionnaire. Data were generated and collected through an internet-based case report form, and anonymously transmitted data were used in analyses. This study was approved by the ethics committee of Samsung Medical Center.

Anthropometric and biochemical measurements

Data were collected from patient medical records and through the comprehensive questionnaire. The following parameters were collected at baseline: age, sex, body composition (weight, height), duration of diabetes, time interval between diagnosis of diabetes and initiation of insulin treatment, regimen of insulin therapy, and total daily dose of insulin. The results of fasting plasma glucose (FPG), HbA1c, total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), blood urea nitrogen, creatinine and spot urine albumin/creatinine ratio were obtained at each visit. We obtained blood samples by venepuncture after an overnight fast, and samples were analyzed by the certified laboratory at each hospital.

Questionnaire-based assessment of hypoglycemia and SMBG frequency

The definition of severe hypoglycemia (SH) was a hypoglycemic event in which another person's assistance was required to escape hypoglycemia. The degree and frequency of hypoglycemia were established at baseline, and changes in the rate of SH during the study period were determined by asking patients whether there were changes in the frequency of SH per month over the past 12 months, and to describe the number of current and previous occurrences of SH per month. The degree of hypoglycemic unawareness at baseline was determined by answers to the following question: "Do you recognize symptoms when you have hypoglycemia?" requiring the selection of one response from "always," "usually," "sometimes" or "never."²¹ Information about SMBG frequency was determined

by asking the following question: "How often do you check your blood glucose per day?" Changes in the frequency of SMBG practice were determined by asking the following question: "Were there changes in the frequency of SMBG over the previous 6 months?; describe current and previous numbers of SMBG per day." The study coordinators interviewed the study participants at 0, 6 and 12 months after baseline. The answers to this question were used to determine if there was an increase in the frequency of SMBG at 6 and 12 months from baseline.

Statistical analysis

Normally distributed data were expressed as mean \pm standard deviation, whereas unevenly distributed data was presented as median (interquartile range: 25th to 75th percentile) for continuous variables. Categorical variables were expressed as number and proportion (%). Student's *t*-test or the non-parametric Mann–Whitney *U*-test was used to compare the means of continuous variables. The categorical variables of the two groups were compared using the χ^2 -test. Differences between the levels of HbA1c and SMBG frequency, and the rate of SH before and after the study period (0 vs 6 months and 0 vs 12 months) were evaluated by the Wilcoxon signed-rank test. Spearman's correlation analysis and non-linear regression were carried out to relate baseline SMBG frequency to HbA1c.

To evaluate factors associated with >5% reduction of HbA1c, decreased rate of SH and increased SMBG frequency at 12 months from baseline, we used a binary logistic regression analyses method. Multivariate binary logistic regression analysis was carried out for variables with a *P*-value <0.2 on univariate analysis in order to identify independent factors associated with >5% reduction of HbA1c, decreased rate of SH and increased SMBG frequency at 12 months from baseline. All statistical tests were two-tailed, and the significance level was set at *P* < 0.05. Analyses were carried out using SPSS (version 18.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics according to the frequency of SMBG

We enrolled 466 adult type 1 diabetes patients in the present prospective cohort study. The study population had a mean age of 43 years, with a mean age of 32 years at the time of diagnosis of diabetes. The baseline characteristics of the study participants are summarized in Table 1. Detailed regimens of insulin therapy were multiple daily insulin for 301 patients (67.9%), continuous subcutaneous insulin infusion for 25 patients (5.6%), premixed biphasic insulin for 71 patients (16.0%), and neutral protamine Hagedorn insulin and regular insulin combination for 46 patients (10.5%). The proportion of patients with intensive insulin therapy (continuous subcutaneous insulin infusion or multiple daily insulin) was unchanged throughout the study period (287 patients, 71.4% at 6 months; 239 patients, 69.1% at 12 months; *P* = 0.377). For study participants whose data were available (*n* = 151), there was no alteration in total daily insulin dosage during the study period (median 0.60 with

an interquartile range [IQR] of 0.47–0.76 U/kg at baseline and median 0.65 with an IQR 0.47–0.82 U/kg at 12 months, *P* = 0.145). Degree of hypoglycemic unawareness at baseline was assessed as "never feel hypoglycemic" in four patients (0.9%), "sometimes feel hypoglycemic" in 100 patients (21.5%), "usually feel hypoglycemic" in 158 patients (33.9%), "always feel hypoglycemic" in 182 patients (39.1%) and "unknown or no response" in 22 patients (3.4%).

Of the 349 patients who answered the SMBG frequency questionnaire, more than half of type 1 diabetes mellitus patients (*n* = 201, 57.6%) carried out SMBG less than two times per day at baseline. Younger age, higher number of female patients, lower baseline HbA1c and a greater proportion of participants receiving intensive insulin therapy, such as multiple daily insulin or continuous subcutaneous insulin infusion, were observed in patients who carried out SMBG four or more times per day (Table 1). In addition, a drop in HbA1c of $0.14 \pm 0.04\%$ for one additional SMBG per day at baseline was observed after adjusting for age, sex, diabetes duration and intensity of insulin therapy (Figure 1; *P* < 0.001).

Factors independently associated with >5% reduction in HbA1c from baseline

A small but significant reduction in HbA1c during the 12-month follow-up period was observed after registration for the reimbursement program. HbA1c at 6 months (median 7.6%, IQR 6.8–8.6; *P* = 0.006) and at 12 months (median 7.7%, IQR 6.8–8.5; *P* = 0.010) decreased from that at baseline (median 7.7%, IQR 6.9–8.8; Figure 2a). The median HbA1c levels around 1 year (mean 12 ± 3 months) before the study entry were 7.9% (IQR 6.9–8.9), which was not different from the HbA1c levels at study entry (*P* = 0.057; *n* = 344). In subgroup analyses according to baseline SMBG frequency, a significant reduction in HbA1c at 6 months (median 7.8%, IQR 7.0–8.9) from baseline (median 7.9%, IQR 7.0–9.1) was observed in patients who carried out SMBG less than four times per day at baseline (*P* = 0.010), but not in those who carried out SMBG four or more times (Figure 2b,c).

At the end of the 12-month follow-up, 158 patients (33.9%) achieved a decrease in HbA1c >5% from baseline. In univariate analysis, baseline higher HbA1c was associated with >5% reduction in HbA1c from baseline. In multivariate analysis, factors independently associated with >5% reduction in HbA1c from baseline were lower total daily insulin dose at baseline (*P* = 0.048), higher baseline HbA1c (*P* < 0.001) and increase in SMBG frequency (*P* = 0.001) during follow up (Table 2).

Factors independently associated with an increase in the frequency of SMBG at 12 months from baseline

Among the 349 patients who answered the questionnaire about SMBG frequency, SMBG frequency at 6 months (median 5.0, IQR 4.0–6.3; *P* < 0.001) and 12 months (median 3.0, IQR 1.0–5.3; *P* < 0.001) increased from that at baseline (median 2.0, IQR 1.0–4.0; *P* < 0.001; Figure 2a). In addition, an increase in

Table 1 | Baseline characteristics of the study sample and comparison between patients who carried out self-monitoring of blood glucose more than four times per day and those who did not

	SMBG <4/day n = 250	SMBG ≥4/day n = 99	Total n = 466	P-value
Age (years)	44 ± 14	38 ± 13	43 ± 14	<0.001
Age at diagnosis (years)	32 ± 14	30 ± 14	32 ± 14	0.089
Sex (men)	136 (54.4%)	32 (32.3%)	230 (49.4%)	<0.001
BMI (kg/m ²)	22.6 ± 2.8	22.4 ± 3.2	22.4 ± 2.9	0.572
Time interval between diagnosis and initiation of insulin (months)	1 (0–7.5)	0 (0–1)	1 (0–3)	0.001
Intensive insulin therapy (MDI or CSII)	163 (66.8%)	85 (88.5%)	326 (70.0%)	<0.001
Total insulin dose (IU/kg/day)	0.56 (0.18–0.76)	0.51 (0.19–0.68)	0.60 (0.47–0.80)	0.373
Baseline SMBG (times/day) [†]	1.5 (1–2)	6 (4–7)	2 (1–4)	<0.001
SBP (mmHg)	121 ± 16	117 ± 15	120 ± 16	0.053
DBP (mmHg)	73 ± 10	72 ± 9	72 ± 10	0.430
FPG (mg/dL)	156 ± 71	147 ± 66	156 ± 73	0.324
Baseline HbA1c (%)	7.9 (7.0–9.1)	7.2 (6.4–8.2)	7.7 (6.9–8.8)	<0.001
12-month HbA1c (%)	7.9 (7.0–8.7)	7.1 (6.5–8.0)	7.7 (6.8–8.5)	<0.001
%Reduction in HbA1c at 12 months from baseline	1.4 (–5.8 to 8.9)	1.2 (–8.0 to 8.9)	1.3 (–6.7 to 9.5)	0.334
C-peptide (ng/mL)	0.16 (0.02–0.51)	0.10 (0.02–0.44)	0.12 (0.02–0.50)	0.174
BUN (mg/dL)	17.3 ± 7.9	16.3 ± 10.0	17.0 ± 8.9	0.498
Creatinine (mg/dL)	0.80 (0.70–0.96)	0.80 (0.66–0.99)	0.80 (0.69–0.96)	0.875
uACR (μg/mg)	12.6 (5.3–44.1)	8.2 (3.3–20.4)	10.2 (4.9–33.8)	0.008
Total cholesterol	172 ± 41	171 ± 37	170 ± 38	0.912
Triglyceride	86 ± 74	85 ± 58	85 ± 66	0.889
HDL-C	62 ± 17	65 ± 19	62 ± 17	0.151
LDL-C	93 ± 27	93 ± 28	93 ± 27	0.996
Rate of SH at baseline (times/month) [†]	1.0 (0.3–2.0)	2.0 (0.0–3.8)	1.0 (0.0–3.0)	0.672
Presence of hypoglycemic unawareness [§]	73 (29.2)	9 (9.1)	104 (22.4)	<0.001
Complications [¶]				
Retinopathy	88 (35.9%)	28 (28.6%)	231 (30.6%)	0.194
Nephropathy	32 (13.1%)	10 (10.2%)	93 (12.5%)	0.458
Neuropathy	57 (24.6%)	40 (42.6%)	249 (33.6%)	0.001

Continuous variables are expressed as median (interquartile range) or mean ± standard deviation, as appropriate. Categorical variables are expressed as number (percentage). [†]n = 349; [‡]n = 148; [§]study participants who reported that they never felt hypoglycemia or sometimes felt hypoglycemia when their glucose is low; n = 444; [¶]retinopathy, individuals who had more than mild non-proliferative diabetic retinopathy documented by ophthalmologists; nephropathy, estimated glomerular filtration rate (by Modification of Diet in Renal Disease Study equation) <60 mL/min/1.72 m²; neuropathy, individuals with history of medication for autonomic neuropathy or peripheral polyneuropathy within one year from baseline. BMI, body-mass index; CSII, continuous subcutaneous insulin infusion; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDI, multiple daily insulin; SBP, systolic blood pressure; SH, severe hypoglycemia; SMBG, self-monitoring of blood glucose; uACR, urine albumin-to-creatinine ratio.

SMBG frequency at 6 and 12 months was observed, regardless of baseline SMBG frequency ($P < 0.001$; Figure 2b,c). The proportion of patients who carried out SMBG four or more times per day increased from 99 of 349 patients (28.4%) at baseline to 154 of 349 (44.1%) at 12 months ($P < 0.001$). In univariate analysis, patients who carried out more frequent SMBG measurement at 12 months than that at baseline were younger, received intensive insulin therapy, had hypoglycemic unawareness and had higher rates of SH at baseline (Table 3). In multivariate analyses, more frequent SMBG measurement ($P = 0.001$), the presence of hypoglycemic unawareness ($P = 0.044$) and more frequent SH ($P = 0.029$) at baseline were independently associated with an increase in the frequency of SMBG at 12 months from baseline (Table 3).

Factors independently associated with a decrease in the rate of SH at 12 months from baseline

Of the 148 patients who answered the questionnaire about the rate of SH, 103 (69.6%) reported that they had experienced one

or more SH events within the past month at baseline. The rate of SH at 6 months (median 1.0 times/month, IQR 0.50–2.0) and at 12 months (median 1.0 times/month, IQR 1.0–2.0) decreased from that at baseline (median 1.0 times/month, IQR 0–3.0; $P < 0.001$; Figure 2a). The rate of SH was decreased in 47 of the 111 patients (42.3%) who had experienced one or more SH events at baseline. In univariate analysis, factors associated with a decreased rate of SH at 12 months were more frequent SMBG measurement and experiences of SH at baseline, lower baseline HbA1c, the presence of hypoglycemic unawareness, and increased frequency of SMBG during the study period. In multivariate analyses, more frequent SMBG measurement at baseline ($P = 0.001$) was independently associated with a decreased rate of SH from baseline (Table 4).

Analysis of adverse event reports

During the study period, the adverse event reports, which were obtained both by reviewing medical records and interviews of study participants by clinical research coordinators, included hypoglycemic episodes requiring admission or visiting the emergency room during the study period. At baseline, 86 patients had a history of hospital admission for various reasons within a year. Among them, 11 patients were admitted for diabetic ketoacidosis management, and 35 patients were admitted or visited the emergency room for controlling severe hypoglycemia. The cumulative number of patients who required admission or an emergency room visit as a result of hypoglycemia during the 1-year study period at 12 months was 19 of the 466 study participants (4.1%). This proportion was significantly lower than that of the study participants who reported admission as a result of hypoglycemia in the recent 1 year at baseline (35 of the 459 study participants, 7.6%; $P < 0.001$).

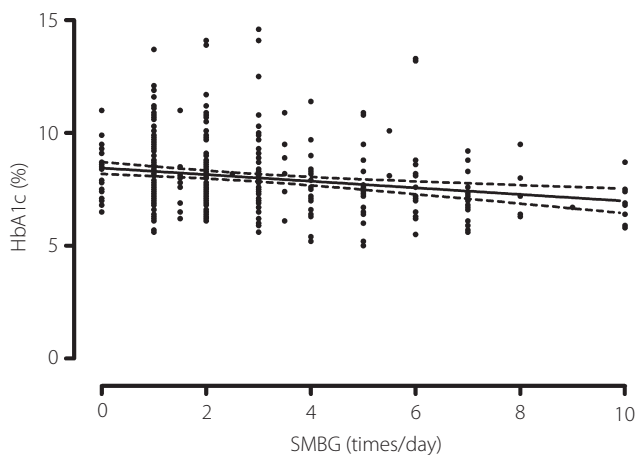


Figure 1 | The correlation between self-monitoring of blood glucose (SMBG) frequency and glycated hemoglobin (HbA1c) at baseline.

DISCUSSION

In the present prospective cohort study, higher baseline HbA1c, lower total daily insulin dose and an increase in SMBG

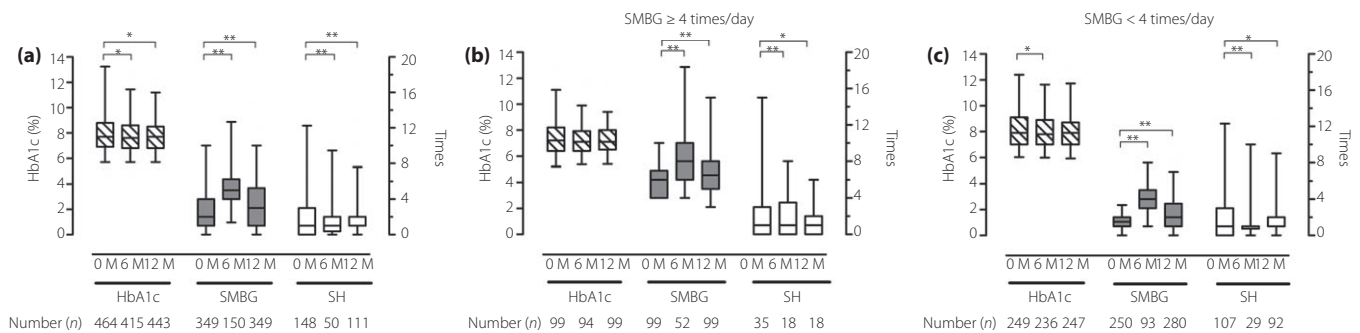


Figure 2 | (a) Overall changes in glycated hemoglobin (HbA1c; %), self-monitoring of blood glucose (SMBG) frequency (times/day) and the rate of severe hypoglycemia (SH; times/month) after registration for the national reimbursement program for blood glucose test strips. (b–c) Changes in HbA1c (%), SMBG frequency and the rate of SH in the subgroups with SMBG frequency at baseline of (b) four or more times/day and (c) less than four times/day. The box-and-whisker plots show the median with interquartile range (box), and the 2.5 percentile and 97.5 percentile values (whisker). * P -value < 0.05 , ** P -value < 0.01 .

Table 2 | Factors associated with >5% reduction in glycated hemoglobin at 12 months from baseline

	Univariate		Multivariate [†]	
	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Baseline SMBG frequency (times/day)	1.01 (0.92–1.11)	0.804		
Changes in SMBG frequency (times/day)	1.16 (1.00–1.34)	0.059	1.38 (1.14–1.68)	0.001
Baseline HbA1c (%)	1.86 (1.60–2.16)	<0.001	2.52 (1.95–3.26)	<0.001
Total daily insulin dose (IU/day/kg)	2.10 (0.89–4.93)	0.090	0.26 (0.07–0.99)	0.048
Rate of SH at baseline (times/month)	0.93 (0.81–1.07)	0.293		
Presence of hypoglycemic unawareness	1.12 (0.71–1.78)	0.618		
Sex (men)	1.17 (0.80–1.71)	0.432		
Age (years)	1.00 (0.98–1.01)	0.206		
Duration of diabetes (years)	1.00 (0.97–1.02)	0.575		
Intensive insulin therapy (MDI or CSII)	0.97 (0.62–1.51)	0.883		

[†]Binary logistic regression analysis. The covariates were included in the multivariate analysis model when the *P*-value was <0.2 in the univariate model. CI, confidence interval; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated hemoglobin; MDI, multiple daily insulin; OR, odds ratio; SH, severe hypoglycemia; SMBG, self-monitoring of blood glucose.

Table 3 | Factors associated with an increase in the frequency of self-monitoring of blood glucose at 12 months from baseline

	Univariate		Multivariate [†]	
	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Baseline SMBG frequency (times/day)	1.09 (1.00–1.20)	0.065	1.35 (1.11–1.65)	0.003
Baseline HbA1c (%)	1.00 (0.87–1.14)	0.977		
Total daily insulin dose (IU/day/kg)	1.04 (0.40–2.71)	0.930		
Rate of SH at baseline (times/month)	1.18 (1.04–1.35)	0.012	1.17 (1.02–1.35)	0.031
Presence of hypoglycemic unawareness	0.46 (0.27–0.79)	0.005	0.34 (0.12–0.97)	0.044
Sex (men)	0.93 (0.60–1.42)	0.725		
Age (years)	0.98 (0.96–0.99)	0.006	1.00 (0.96–1.03)	0.842
Duration of diabetes (years)	0.99 (0.96–1.01)	0.246		
Intensive insulin therapy (MDI or CSII)	2.33 (1.38–3.96)	0.002	1.62 (0.56–4.70)	0.379

[†]Binary logistic regression analysis. The covariates were included in the multivariate analysis model when the *P*-value was <0.2 in the univariate model. BMI, body mass index; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated hemoglobin; MDI, multiple daily insulin; OR, odds ratio; SH, severe hypoglycemia; SMBG, self-monitoring of blood glucose.

frequency during follow up were independently associated with >5% reduction in HbA1c. Higher SMBG frequency at baseline and a higher rate of SH at baseline were independently associated with an increase in the frequency of SMBG at 12 months from baseline. Higher SMBG frequency at baseline was independently associated with a decreased rate of SH.

The participants evaluated in the present study were predominantly patients with adult-onset type 1 diabetes mellitus, in contrast to previous studies in Western countries that mostly included people aged <18 years^{2,22}. The vast majority of our study sample had clinical features of typical type 1 diabetes mellitus rather than latent autoimmune diabetes of adults, evaluated in terms of the time interval between diagnosis and initiation of insulin. Analyses of baseline characteristics in the present study showed a close association between the frequency of SMBG and HbA1c in type 1 diabetes mellitus adult patients after adjusting for demographic and anthropometric

confounders. This result is consistent with those of previous studies in which the majority of the study sample was made up of individuals with child-onset type 1 diabetes mellitus; these individuals experienced a 0.20–0.26% drop in HbA1c per each additional daily SMBG^{2,23}. Among these previous studies, analysis of the T1D Exchange Clinic Registry (*n* = 20,555) showed that mean HbA1c was approximately 9.0% in adult participants (age of 26–50 years) with an SMBG frequency of zero to two per day, and approximately 8.5% in those with an SMBG frequency of three to four per day²². In adult participants of the T1D Exchange Clinic Registry aged >50 years, the mean HbA1c was approximately 8.5% in those with an SMBG frequency of zero to two per day, and approximately 8.2% in those with an SMBG frequency of three to four per day²². Because the reimbursement policy in the present study covered up to four SMBGs per day, we expected the reduction in HbA1c might be similar to that of the difference in HbA1c

Table 4 | Factors associated with a decreased rate of severe hypoglycemia at 12 months from baseline

	Univariate		Multivariate [†]	
	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Baseline SMBG frequency (times/day)	2.63 (1.71–4.04)	<0.001	2.15 (1.35–3.43)	0.001
Change in SMBG frequency (times/day)	1.97 (1.35–2.88)	<0.001	1.09 (0.75–1.58)	0.649
Baseline HbA1c (%)	0.78 (0.62–0.99)	0.047	0.88 (0.68–1.13)	0.312
Total daily insulin dose (IU/day/kg)	0.86 (0.19–3.91)	0.848		
Rate of SH at baseline (times/month)	1.32 (1.08–1.62)	0.007	1.12 (0.91–1.37)	0.284
Presence of hypoglycemic unawareness	0.28 (0.11–0.70)	0.007	0.47 (0.16–1.41)	0.179
Sex (men)	0.71 (0.33–1.50)	0.366		
Age (years)	1.00 (0.97–1.03)	0.787		
Duration of diabetes (years)	1.00 (0.96–1.04)	0.953		
Intensive insulin therapy (MDI or CSII)	0.65 (0.27–1.55)	0.330		

[†]Binary logistic regression analysis. The covariates were included in the multivariate analysis model when the *P*-value was <0.2 in the univariate model. CI, confidence interval; CSII, continuous subcutaneous insulin injection; HbA1c, glycated haemoglobin; MDI, multiple daily insulin; OR, odds ratio; SMBG, self-monitoring of blood glucose.

between those with an SMBG frequency of zero to two per day and three to four per day as reported in the T1D Exchange Clinic Registry. Therefore, we chose a 5% reduction in HbA1c as the cut-off value for a significant reduction in HbA1c during the study period.

In the present study, a lower total daily insulin dose was independently associated with a > 5% reduction in HbA1c during the study period after adjustment for changes in SMBG frequency and baseline HbA1c (Table 2). Notably, ≥25% of the study participants with an SMBG frequency of less than four times per day and four or more times per day in the present study had a total daily insulin dose of <0.2 IU/kg/day (Table 1). In a previous study²⁴, there was a U-shaped association between 18-month average HbA1c and body mass index in Korean patients with type 1 diabetes. In that study, the higher HbA1c in the study participants with lower body mass index was explained by the use of an inadequately low dose of insulin in participants with high insulin sensitivity, for whom even small errors in insulin dosing could result in severe changes in blood glucose level. Although patients with extremely low total daily insulin doses frequently require adjustment of <1 unit dose for mealtime bolus insulin, adjustment of a < 1 unit dose of insulin is not possible in most Korean people with type 1 diabetes, because insulin pumps are not insured in Korea²⁵. Therefore, it is possible that study participants with low total daily insulin doses in the current study could include patients for whom adjustment of insulin dose was most challenging, for whom increasing the SMBG frequency would be most helpful for better glucose control.

In the present study, a higher rate of prior SH at baseline was independently associated with an increased frequency of SMBG practice during the study period. Higher rates of prior SH at baseline might motivate individuals to increase SMBG frequency. Ziegler *et al.*² reported that the rate of hypoglycemia was positively associated with the frequency of daily SMBG

among 267,232 children and adolescents with type 1 diabetes mellitus, which shows that experience with hypoglycemia is likely to encourage patients to monitor their blood glucose levels more frequently. The participants in the current study who had prior experience of SH at baseline might have been more motivated than the other patients to increase their SMBG frequency, and be more likely to benefit from the reimbursement policy.

The independent association between the presence of hypoglycemic unawareness and lack of increase in the frequency of SMBG during the study period (Table 3) is an unexpected finding. As we used a simple screening questionnaire that was used in several previous studies²¹, we speculate that these results are not confirmatory and should be validated in further studies using a more intensive scoring system, such as Clarke or Gold scores^{26,27}. If confirmed in further studies, the results might show that reimbursement of the test strips without additional support for the stepwise approach to problematic hypoglycemia²⁶ is not effective in patients with hypoglycemic unawareness, because these patients require more intervention than simply reducing the cost of SMBG. Rather than simply increasing SMBG frequency, a stepwise approach starting from a structural education typically requiring a 30- to 4-h group learning curriculum, and then use of a technological approach, such as real-time continuous glucose monitoring and/or an insulin pump, and finally islet or pancreas transplantation, has been recommended for these patients²⁶.

The independent association between higher SMBG frequency at baseline and both the increase in SMBG frequency and decrease in the rate of SH during the study period is another novel finding of the present study. In the analysis of the 20,555 participants of the T1D Exchange Clinic Registry²², a continuous trend toward lower mean HbA1c was observed with increasing SMBG frequency (up to 10 per day). Recent guidelines suggest very frequent (6 to ≥10 times daily including

before meals, before exercise, at bedtime, upon suspected hypoglycemia and before driving) SMBG in most patients on intensive insulin regimens^{5,7}. The results of the current study suggest that an increase in the frequency of SMBG in motivated patients who already carry out SMBG more frequently at baseline is one of the most important benefits of the national reimbursement policy.

There were several limitations to the present study that should be discussed. First, our results were drawn from patients enrolled at just five hospitals, and were not representative of all type 1 diabetes mellitus Korean patients. Therefore, the results of the present study should not be extrapolated to patients in primary care settings. Second, the SH and SMBG frequencies were self-reported, and subjective recall could have biased the results. Although it has been observed that analysis based on self-reported SMBG measurements per day and the analytic results of the data from clinic meter downloads were similar in the participants subset of the T1D Exchange Clinic Registry²² and we used a questionnaire similar to that used in the T1D Exchange Clinic Registry, we did not validate our study population due to the lack of availability of clinical meter downloads data. Therefore, the present study shares the limitation of lacking objective measurement of SMBG frequency with several previous questionnaire-based outpatient studies^{22,28}. Third, changes in dietary and exercise behaviors after adopting a reimbursement policy was not assessed in the study.

In conclusion, several factors, including higher SMBG frequency at baseline, were independently associated with greater effectiveness of the KNHIS reimbursement program in terms of decreasing HbA1c level and the frequency of severe hypoglycemia. These results can potentially be used to identify those patients that might benefit most from reimbursement for glucose test strips for SMBG.

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DISCLOSURE

The authors declare no conflict of interest.

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