The Influence of Self-monitoring Blood Glucose Frequency on the Oscillation of Hemoglobin A1c and Chronic Complications

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Background: A fluctuating blood glucose level is one of the risks of chronic complications in diabetes. Previous studies indicated that hemoglobin A1c (HbA1c) values apparently improved after initiation of self-monitoring blood glucose (SMBG). The purpose of this study is to investigate the relationship between the frequency of SMBG, long-term fluctuatation of HbA1c, and risks of chronic complications in diabetes.

Methods: We enrolled 1052 patients with type 2 diabetes. The mean follow-up was 4.7 years. The HbA1c level and frequency of SMBG were recorded every 3 months. Non-mydriatic retinal photography, semiquantitative neuropathy assessment, the lipid profile, serum creatinine level, and urine protein were measured at the beginning of the study and then every year. The fluctuation in HbA1c throughout the period was expressed as the standard deviations (SDs) of all measurements of the HbA1c.

Results: The frequency of SMBG was significantly and negatively correlated with the SDs of the HbA1c (r = –0.553, $p < 0.001$) but not with the average HbA1c. After controlling for age, sex, body mass index, duration of diabetes and comorbidities (dyslipidemia and hypertension), the correlation was still apparent (r = –0.511, $p = 0.008$). Patients with progression of nephropathy, neuropathy, and retinopathy, exhibited greater fluctuation of HbA1cs (2.38 ± 0.99 vs. 0.93 ± 1.16, *p*-value 0.002; 0.97 ± 1.59 vs. 0.90 ± 0.56, *p*-value 0.04; 0.99 ± 1.33 vs. 0.90 ± 0.56, *p*-value 0.04, respectively) and less frequent SMBG (3.2 ± 2.6 vs. 4.3 ± 3.1, *p*-value 0.02; 3.2 ± 2.6 vs. 4.1 ± 3.9, *p*-value 0.05; 3.0 ± 3.1 vs. 4.2 ± 2.8, *p*-value 0.01, respectively) than patients without progression of these complications.

Conclusion: This study shows that frequent SMBG decreased the fluctuation of HbA1c and decreased microvascular complications. Decreasing fluctuation of HbA1c may play an important role in diabetes treatment.

(Chang Gung Med J 2012;35:46-53)

Key words: self-monitoring blood glucose, oscillation of hemoglobin A1c

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Received: Jan. 27, 2011; Accepted: Jul. 15, 2011
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Variation in blood glucose levels leads to an overproduction of free radicals and oxidative stress, especially in patients with type 2 diabetes.[1-3] The oxidative stress induced by fluctuating blood glucose levels increases the risk of microvascular and macrovascular complications. In a type 1 diabetes study, the Diabetes Control and Complications Trial (DCCT), long-term oscillation of blood glucose levels instead of short-term (within a day) seemed to contribute to the development of these chronic complications.[4,5] Data from the Pittsburgh Epidemiology Study revealed that fluctuating hemoglobin A1C (HbA1c) is an additional risk factor for the development of macrovascular complications in type 1 diabetes.[6] To prevent these diabetes complications, some therapeutic agents can act on postprandial glucose excursions to reduce glucose fluctuations.[7]

Self-monitoring blood glucose (SMBG) is also an important therapy for diabetes mellitus (DM) and helps patients with poor metabolic control. This approach can be used to adjust the therapeutic regimen according to blood glucose levels, helping patients adjust their dietary intake, physical activity, and medication. It could improve glycemic control on a day-to-day or week-to-week basis. Previous studies revealed that initiating SMBG improves HbA1c values.[8,9] It is important to know whether frequent monitoring of blood glucose levels actually decreases the variability of HbA1c, which may in turn reduce progression of chronic complications.

METHODS

Subjects

We followed 1052 patients with type 2 DM (520 women and 532 men, age 56.6 ± 11.4 years) at our outpatient clinic from 2004 to 2010. We excluded any patient who smoked or had cardiogenic shock, unstable angina, stroke, and myocardial infarction during the follow-up period, renal function impairment (creatinine level > 1.4 mg/dl), peptic ulcer history, cancer, hemoglobinopathy history, systemic inflammatory disease and history of insulin injections for more than 2 weeks. All patients had established type 2 DM for more than 1 year and had received oral antidiabetic drugs (OAD) for more than 1 month. The mean follow-up was 4.7 ± 1.4 years. All patients were confirmed to have type 2 DM based on 2005 American Diabetes Association diagnostic criteria. They all participated in sequential and regular diabetic education programs to standardize education in diabetes management and visited a dietician every 3 months for more than 2 years. The education program was performed by a diabetic educator and dietician certificated by the Taiwanese Association of Diabetes Educators. Self-monitoring of blood glucose at home was also recommended. All of these patients also received SMBG education the first time they visitied the educators and all of them had blood glucose meters. The accuracy of SMBG was checked at the second visit, They also received a scheduled, sequenced education program which included hypoglycemia and hyperglycemia self-management, prevention and management of DM chronic complications, foot care coaching, sick-day management, nutrition therapy, and exercise. Because all of these participants received OAD, they were taught how to decrease their dose of sulfonylureas when they had symptoms of hypoglycemia or a blood glucose less than 70 mg/dl on the blood glucose meter. For hypoglycemia, patients were instructed to begin with 15 to 20 grams of carbohydrates (1/2 cup juice or a regular soft drink, 3 to 4 glucose tabs, or 8 to 10 hard candies), and then recheck the blood glucose after 15 minutes. We also recommended repeating hypoglycemia treatment if the blood glucose did not return to the normal range after 15 minutes, followed by additional carbohydrates or a snack if the next meal was more than one hour away. If hypoglycemia persisted after the second treatment, the patient or a companion was instructed to contact a healthcare provider. HbA1c was measured every 3 months. All diabetes complications were checked and recorded every year. The frequency of SMBG was defined as the average number of blood glucose measurements using a blood glucose meter each week and this data was recorded during clinic visits every 3 months. A history of hypertension and dyslipidemia was recorded from patient medical histories.

Methods

The following clinical and laboratory parameters were measured at the beginning of the study and every year: body mass index (BMI), non-mydriatic fundusgraphy and semiquantitative neuropathy assessment serum levels of the total cholesterol (TC), low-density lipoprotein (LDL), high-density lipopro-

tein (HDL), triglycerides (TG), and creatinine (Cr), and urine protein.

Protective sensation was assessed using the 5.07 Semmes-Weinstein (SW, 10-g) nylon filament test (10-g monofilament test) and vibration perception using a 128 Hz Rydel-Seiffer fork. Two observers confirmed all measurements. Neuropathy was evaluated based on the vibration perception threshold at the big toe and internal malleolus of both feet. The patients were asked to respond if they could no longer feel the vibration. The vibration was determined on the 9-point grading scale (0/8–8/8) of a tuning fork. Patients were diagnosed with neuropathy if the vibration perception thresholds were inferior or equal to 4/8.[10] The vibration perception thresholds yielded a sensitivity of 86% and a specificity of 76%.[11]

Two examiners conducted the SW monofilament test when patients were unable to observe their feet. The 10 g SW monofilament was used on ten sites on the foot (dorsal surface of the foot between the base of the first and second toes; the first, third and fifth toes; the first, third and fifth metatarsal heads; the medial and lateral midfoot, and the heel). The SW monofilament was pressed on the test site with enough pressure to bend the monofilament for 1 sec. Patients were asked to answer "Yes or No" when they felt or did not feel the touch of the monofilament, respectively. If a patient did not feel the filament at more than 4 sites, neuropathy was diagnosed. The sensitivity at ten sites with a 10 g SW monofilament was 93.1% and the specificity was 100%.[12]

Non-mydriatic retinal photography was performed using a CR6–45NM non-mydriatic retinal camera Canon by two examiners. Retinopathy was diagnosed according to the American Academy of Ophthalmology Retina/Vitreous Panel, Preferred Practice Patterns Committee and was also confirmed by one ophthalmologist.[13] The effectiveness of the non-mydriatic retinal camera in the diagnosis of retinal disease had a sensitivity of 92% and a specificity of 96%.[14] Nephropathy was defined as an increase in urine protein > 30 mg/dl in a first morning void spot urine sample.[15] The sensitivity was 100% and specificity was 76.2% for urinary protein.[16] Progression of chronic complications was determined according to records from the last examination compared with those from the initial examination. Progression of neuropathy was defined as protective sensation and vibration sensation which were normal at the beginning of the study but abnormal at the last examination. Progression of retinopathy was defined as progression from a low stage to a higher stage of retinopathy. Progression of nephropathy was defined as an increase in proteinuria at the last examination.

In addition to measuring the mean HbA1c, we calculated the variability of the HbA1c throughout the period, and expressed the results as the SDs of all measurements of the HbA1c. Because the HbA1c levels apparently changed after the first intervention, the SDs were calculated based on the values taken after the initial measuring point.

This study was conducted according to the guidelines of the Declaration of Helsinki, and the research protocol was approved by the Ethics Committee of Chang Gung Memorial Hospital.

Assays

The concentrations of TC, LDL, HDL, TG, and Cr were measured using an autoanalyzer (Hitachi 7250 Special; Hitachi, Tokyo, Japan). Urine protein was measured by the protein pad on a multi-reagent dipstick (Multistix® SySy International Hungary Ltd). The HbA1c level was measured by high-pressure liquid chromatography (Bio-Rad Laboratories, Inc, Richmond, CA, U.S.A.).

Statistical analysis

The variables were summarized as mean ± SD. Differences in baseline clinical and biochemical characteristics were tested using an unpaired *t*-test. Spearman correlation analysis was performed to relate the SD of the HbA1C to the frequency of SMBG. Controlling for age, sex, BMI, duration of diabetes and comorbidities (dyslipdemia and hypertension) at the last visit, we also used partial correlation coefficients to assay the relationship between the SD of the HbA1c, progression of chronic complications and the frequency of SMBG. A p value of < 0.05 was considered statistically significant.

RESULTS

Table 1 reveals the clinical characteristics of these 1052 type 2 DM patients. After the education program, the HbA1c decreased significantly (8.7 ± 2.1 to 7.5 ± 1.2). There were 13 to 24 measurements of HbA1c recorded in every patient (17.6 ± 5.2).

Table 1. The Clinical Characteristics of 1052 Patients with Type 2 DM

Clinical characteristics	Beginning of study	Last examination	*p* value
Age (years)	56.6 ± 11.4		
Patients (Female/Male)	1052 (520/532)		
Diabetes duration			
< 5 years	20.2%		
5-10 years	27.6%		
11-15 years	26.3%		
> 15 years	25.9%		
OAD (kind)			
One	14.0%	12.2%	0.05
Two	55.4%	53.6%	NS
Three or more	30.6%	34.2%	0.02
HbA1c (%)	8.7 ± 2.1	7.5 ± 1.2	< 0.001
Cholesteral. (mg/dl)	191.1 ± 42.8	181.2 ± 32.2	0.02
HDL (mg/dl)	47.8 ± 12.2	48.3 ± 11.2	NS
LDL (mg/dl)	117.0 ± 35.7	110 ± 30.3	0.04
Triglycerides (mg/dl)	157.4 ± 142.0	133 ± 99.2	0.01
SMBG (times/week)	2.1 ± 1.8	4.1 ± 4.0	< 0.001
Neuropathy	30.3%	44%	< 0.001
Retinopathy			
Normal	63.3%	56.5%	0.006
BDR	24.5%	29.8%	0.001
Pre-PDR	8.4%	9.1%	NS
PDR	3.8%	4.6%	0.05
Nephropathy			
No proteinuria	60.1%	50.4%	0.005
Proteinuria: 30-300 mg/dl	28.2%	34.1%	0.02
Proteinuria: > 300 mg/dl	11.7%	15.5%	0.01

Abbreviations: OAD: oral antidiabetic drugs; LDL: low-density lipoprotein; HDL: high-density lipoprotein; SMBG: self-monitoring blood glucose; BDR: background diabetic retinopathy; PDR: proliferative diabetic retinopathy; DM: diabetes mellitus; Hb: hemoglobin.

During the follow-up period, no participants had acute complications or were admitted to the hospital.

The frequency of blood glucose testing by patients was significantly and negatively correlated with the SDs of the HbA1c (r = –0.553, $p < 0.001$, Figure), but not with the average HbA1c (r = 0.025, $p = 0.307$). After controlling for age, sex, BMI, duration of diabetes and comorbidities (dyslipdemia and hypertension), the frequency of blood glucose testing by patients was still negatively correlated with the SDs of the HbA1c (r = –0.511, $p = 0.008$), but not with the average HbA1c (r = 0.069, $p = 0.440$). The frequency of SMBG was also correlated with progression of nephropathy (r = –0.49, $p = 0.02$), neuropathy (r = –0.37, $p = 0.04$), and retinopathy (r = –0.61, $p = 0.006$).

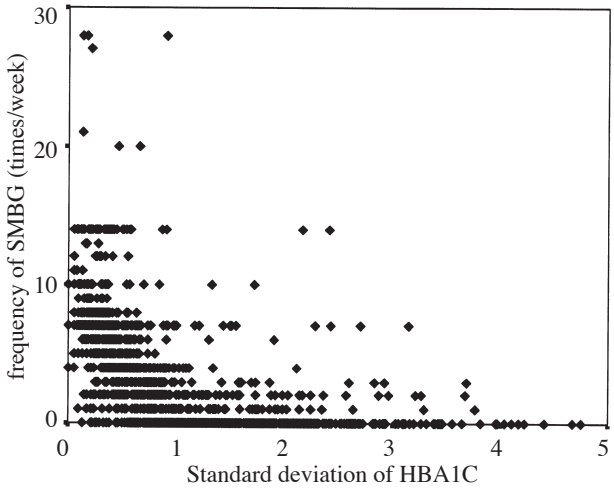

Figure Relationship between oscillation of HbA1C (SD) and frequency of self-monitoring blood glucose (SMBG) r = –0.553, $p < 0.001$.

Patients with progression of nephropathy (14.2%), neuropathy (13.7%), and retinopathy (6.8%) exhibited greater fluctuation in blood glucose levels (SDs) than patients without these complications (2.38 ± 0.99 vs. 0.93 ± 1.16, *p*-value 0.002; 0.97 ± 1.59 vs. 0.90 ± 0.56, *p*-value 0.04; 0.99 ± 1.33 vs. 0.90 ± 0.56, *p*-value 0.04, respectively, Tables 2-4).

The frequency of SMBG was lower in patients with progression of nephropathy, neuropathy, and retinopathy, than patients without progression of these complications (3.2 ± 2.6 vs. 4.3 ± 3.1, *p*-value 0.02; 3.2 ± 2.6 vs. 4.1 ± 3.9, *p*-value 0.05; 3.0 ± 3.1 vs. 4.2 ± 2.8, *p*-value 0.01, respectively, Tables 2 - 4). There were no apparent differences in the the number of oral hypoglycemia agents, hypertension or dyslipidemia between patients with and without progression of microvascular complications. Changes in the BMI, TC, LDL, HDL, TG and blood pressure were also not different between these two groups.

Table 2. Comparison of Fluctuation of Blood Glucose Levels and Frequency of SMBG between Patients with and without Progression of Nephropathy

	Nephropathy	Non-nephropathy	*p* value
Number	149 (14.2%)	903	
Age	61.4 ± 10.9	55.4 ± 12.4	0.06
SMBG	3.2 ± 2.6	4.3 ± 3.1	0.02
SD HbA1cs	2.38 ± 0.99	0.93 ± 1.16	0.002
HbA1c (average)	7.6 ± 3.6	7.1 ± 1.7	NS
Hypertension	60%	49%	0.05
Dyslipidemia	45%	52%	NS
OAD (kind)			
One	15.4%	14.2%	NS
Two	53.5%	53.6%	NS
Three or more	31.1%	32.2%	NS

Abbreviations: SMBG: self-monitoring blood glucose; OAD: oral antidiabetic drugs; SD: standard deviation; HbA1c: hemoglobulin A1c.

Table 3. Comparison of Fluctuation of Blood Glucose Levels and Frequency of SMBG between Patients with and without Progression of Neuropathy

	Nephropathy	Non-nephropathy	*p* value
Number	144 (13.7%)	908	
Age	62.4 ± 11.9	54.8 ± 10.9	0.04
SMBG	3.2 ± 2.6	4.1 ± 3.9	0.05
SD of HbA1cs	0.97 ± 1.59	0.90 ± 0.56	0.04
HbA1c (average)	7.6 ± 1.3	7.8 ± 1.6	NS
Hypertension	51%	49%	NS
Dyslipidemia	43%	46%	NS
OAD (kind)			
One	17.4%	18.2%	NS
Two	49.0%	51.2%	NS
Three or more	33.6%	30.6%	0.05

Abbreviations: SMBG: self-monitoring blood glucose; OAD: oral antidiabetic drugs; SD: standard deviation; HbA1c: hemoglobulin A1c.

Table 4. Comparison of Fluctuation of Blood Glucose Levels and Frequency of SMBG between Patients with and without Progression of Retinopathy

	Retinopathy	Non-retinopathy	*p* value
Number	72 (6.8%)	980	
Age	60.4 ± 11.2	55.6 ± 13.7	0.07
SMBG	3.0 ± 3.1	4.2 ± 2.8	0.01
SD HbA1cs	0.99 ± 1.33	0.90 ± 0.56	0.04
HbA1c (average)	7.7 ± 1.7	7.8 ± 2.0	NS
Hypertension	49%	51%	NS
Dyslipidemia	44%	41%	NS
OAD (kind)			
One	13.3%	11.7%	NS
Two	60.2%	62.7%	NS
Three or more	26.6%	25.6%	NS

Abbreviations: SMBG: self-monitoring blood glucose; OAD: oral antidiabetic drugs; SD: standard deviation; HbA1c: hemoglobulin A1c.

DISCUSSION

In addition to fasting blood glucose and postprandial blood glucose, this study recognized glycemic variability as a third component of dysglycemia in diabetes.[17] HbA1c reflects mean glycemic control but is not meaningfully affected by glycemic instability. Oscillating blood glucose levels can damage endothelial function and induce oxidative stress more than a consistently high blood glucose.[1,18] Choi et al. showed that oxidative stress is a key factor in the development of diabetic complications.[19] However, previous animal and human studies showed no direct link between acute hyperglycemia and oxidative stress. Thus, short-term changes in blood glucose levels may not be enough to induce cell damage. Further investigation is necessary to determine whether long-term variability plays a more important role than short-term oscillation. Previous research revealed that a 1% absolute increase in the HbA1c SD doubles retinopathy and yields an 80% increase in the risk of nephropathy.[4] In patients with type 1 diabetes, HbA1c fluctuation can predict the incidence of microalbuminuria, the

progression of renal disease and the incidence of cardiovascular disease events.[5] Previous DCCT research revealed that variation in the long-term HbA1c, defined as interpersonal SDs of quarterly measured HbA1c, is also related to nephropathy and retinopathy.[4] Previous study also showed a relationship between changes in the HbA1c and macrovascular disease in type 1 diabetic groups.[6] The current study focused on patients with type 2 DM who received the same diabetic education and OAD treatment. Although it only included short term (mean 4.7 years) observation, this study showed that progression of chronic complications is related to fluctuation in the HbA1c instead of the average value of the HbA1c.

This study further showed that frequent SMBG could decrease the variability of HbA1cs. While the frequency of SMBG was not related to the mean HbA1c levels, a high frequency of SMBG apparently improved blood glucose stability. Decreasing chronic complications may occur primarily because of decreasing oscillation of HbA1c via frequent SMBG. Continuous motivation to get better control may play the most important role. Fifteen years ago, the guidelines of the French Association ALFEDIAM (Association de Langue Française pour l'Etude du Diabète et des Maladies métaboliques) revealed that SMBG may have three benefits in type 2 DM: (1) increases compliance with diet and exercise; (2) helps with initiation or close adjustment of sulfonylurea therapy; and (3) helps with prescription of antidiabetic drugs during inter-current disease.[20] In 2009, the International Diabetes Federation suggested that SMBG is likely to be an effective self-management tool. Two meta-analyses revealed that non-insulin-receiving patients with type 2 diabetes had significantly greater reductions in HbA1c levels when SMBG was included.[21,22] SMBG can decrease diabetes-related morbidity and all-cause mortality in type 2 diabetes, and may be associated with a healthier lifestyle and/or better disease management.[23]

Previous studies of the effect of SMBG on people with type 2 diabetes have produced conflicting results.[24-27] A small sample size and sampling patients nearing target control makes a decrease in the HbA1c difficult to detect. Fluctuating glycemic levels were also not evaluated. SMBG may be of limited effectiveness in improving glycemic control in patients without appropriate education. All our patients received regular education, performed the SMBG technique accurately, and were educated about self–adjusting oral hypoglycemic agents. Therefore, the changes in the HbA1c were significantly correlated with the frequency of SMBG, and oscillation in the HbA1c was also negatively correlated.

Conclusion

These results show that frequent SMBG could reduce chronic complications and improve the quality of life of patients with type 2 diabetes. However, the lack of long-term longitudinal observation and an average frequency of only 4 SMBG measurements per week in our non- progression group were limitations in this study. Decreasing variability in the HbA1c may play an important role in DM treatment except for the fasting and postprandial glucose.

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血糖自我監測的頻率對糖化血色素的變動及慢性併發症的影響

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背 景： 血糖濃度的變動是糖尿病大小血管併發症的危險因子之一，而過去的研究發現血糖自我監測可以改善病人的糖化血色素，本篇報告的目的在於研究血糖自我監測和糖化血色素的變動及慢性併發症的關係。

方 法： 本研究收錄了 1052 位第二型糖尿病病人，平均追蹤 4.7 年。每三個月紀錄一次病人的糖化血色素值及血糖自我監測的次數，並於研究一開始及每年幫病人做視網膜檢查，半定量神經病變檢查，及膽固醇、肌酸酐、尿蛋白的檢測。糖化血色素的變動以所有糖化血色素測量值的標準差來表示。

結 果： 血糖自我監測的頻率跟糖化血色素的標準差呈現負相關性 (r = –0.553, *p* 值 < 0.001)，但與糖化血色素的平均值則無相關。腎病變、神經病變、視網膜病變惡化的病人，其糖化血色素的變動比未惡化的病人來得大 (糖化血色素的標準差分別爲 2.38 ± 0.99 vs. 0.93 ± 1.16，*p* 值 0.002；0.97 ± 1.59 vs. 0.90 ± 0.56，*p* 值 0.04；0.99 ± 1.33 vs. 0.90 ± 0.56，*p* 值 0.04)，且血糖自我監測的頻率也比未惡化的病人來的低 (血糖自我監測次數的平均值分別爲 3.2 ± 2.6 vs. 4.3 ± 3.1，*p* 值 0.02；3.2 ± 2.6 vs. 4.1 ± 3.9，*p* 值 0.05；3.0 ± 3.1 vs. 4.2 ± 2.8，*p* 值 0.01)。

結 論： 血糖自我監測的次數愈多可以減少糖化血色素的變動及小血管併發症的惡化。減少糖化血色素的變動在糖尿病的治療上可能扮演一個重要的角色。

(長庚醫誌 2012;35:46-53)

關鍵詞： 血糖自我監測，糖化血色素的變動

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受文日期：民國100年1月27日；接受刊載：民國100年7月15日
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