

Long-Term Effect of the Internet-Based Glucose Monitoring System on HbA_{1c} Reduction and Glucose Stability

A 30-month follow-up study for diabetes management with a ubiquitous medical care system

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OBJECTIVE — To investigate the long-term effectiveness of the Internet-based glucose monitoring system (IBGMS) on glucose control in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We conducted a prospective, randomized, controlled trial in 80 patients with type 2 diabetes for 30 months. The intervention group was treated with the IBGMS, while the control group made conventional office visits only. HbA_{1c} (A1C) was performed at 3-month intervals. For measuring of the stability of glucose control, the SD value of A1C levels for each subject was used as the A1C fluctuation index (HFI).

RESULTS — The mean A1C and HFI were significantly lower in the intervention group ($n = 40$) than in the control group ($n = 40$). (A1C [mean \pm SD] 6.9 ± 0.9 vs. $7.5 \pm 1.0\%$, $P = 0.009$; HFI 0.47 ± 0.23 vs. 0.78 ± 0.51 , $P = 0.001$; intervention versus control groups, respectively). Patients in the intervention group with a basal A1C $\geq 7\%$ ($n = 27$) had markedly lower A1C levels than corresponding patients in the control group during the first 3 months and maintained more stable levels throughout the study ($P = 0.022$). Control patients with a basal A1C $< 7\%$ ($n = 15$) showed the characteristic bimodal distribution of A1C levels, whereas the A1C levels in the intervention group remained stable throughout the study with low HFI.

CONCLUSIONS — Long-term use of the IBGMS has proven to be superior to conventional diabetes care systems based on office visits for controlling blood glucose and achieving glucose stability.

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Many controlled clinical trials have shown that prolonged maintenance of the appropriate HbA_{1c} (A1C) level reduces the risk of developing diabetes complications in individuals

with type 1 and type 2 diabetes (1–3). However, data from the National Health and Nutrition Examination Surveys in the U.S. showed that overall glycemic control did not improve between the assessment

periods of 1988–1994 and 1999–2000 (4,5). Similar findings have been reported in other countries (6,7).

Therefore, to achieve and maintain the target level of A1C, new approaches for a medical delivery system are necessary. For this purpose, different strategies using electronic technologies or educational programs have been proposed to improve the quality and efficiency of care for people with diabetes (8–15). In our previous study (16), we introduced a new bidirectional communication tool for diabetes management referred to as the Internet-based glucose monitoring system (IBGMS) and demonstrated its short-term effects over 3 months. The IBGMS comprises an electronically organized circuit for diabetes management that includes both online and offline systems. This management system provides a close doctor-patient relationship, offers more educational opportunities, and enhances patient feedback.

In this study, we demonstrated the long-term effectiveness of the IBGMS on glucose stability and A1C reduction.

RESEARCH DESIGN AND METHODS

Initially, 120 individuals with type 2 diabetes were screened by a review of their medical records at Kangnam St. Mary's Hospital Diabetes Center. Inclusion criteria included patients ≥ 30 years of age who had been followed up for > 6 months in the center. Criteria for exclusion included disabling conditions or diseases such as heart failure, hepatic dysfunction, a creatinine level > 0.133 mmol/l, severe complications of diabetes, or treatment with an intensified insulin regimen.

All patients were interviewed initially, and those who did not have Internet access in their homes or offices, did not know how to use the Internet, or did not wish to participate in the study were excluded. Patients were also excluded if they had any history of participating in other programs that provided similar in-

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Abbreviations: HFI, HbA_{1c} fluctuation index; GC, good compliance; IBGMS, Internet-based blood glucose monitoring system; PC, poor compliance; SMBG self-monitoring of blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Clinical characteristics of subjects

Characteristics	Control	Intervention	P
n	40	40	
Age (years)	54.6 ± 8.6	51.3 ± 9.1	0.098
Sex (M/F)	23/17	26/14	0.647
Diabetes duration (years)	6.9 ± 5.7	6.7 ± 5.3	0.868
Hypertension	13 (32.5)	11 (27.5)	0.808
BMI (kg/m ²)	23.8 ± 2.8	22.8 ± 2.6	0.139
SBP (mmHg)	128.5 ± 16.1	121.3 ± 16.5	0.070
DBP (mmHg)	77.2 ± 9.1	74.0 ± 11.6	0.187
Glucose control methods (n)			0.683
Lifestyle modification	3	4	
Oral medication only	30	25	
Oral medication + insulin	3	5	
Insulin only	4	6	

Data are means ± SD or n (%) unless otherwise indicated. DBP, diastolic blood pressure; SBP, systolic blood pressure.

formation or if they received diabetes management education from any Web site other than our own. Finally, 80 individuals who met all criteria were enrolled.

Upon enrollment and after providing written informed consent, each participant was assigned to either the intervention or control group ($n = 40$ in each) using adaptive randomization. The study protocol was reviewed and approved by the review board of our institution.

All participants were asked to visit the Kangam St. Mary's Hospital Diabetes Center for measurement of their weight, height, and blood pressure and were given glucometers. A1C was measured by high-performance liquid chromatography (Variant II A1C analyzer; Bio-Rad, Montreal, Quebec, Canada). A fasting blood sample was obtained to measure the concentrations of plasma glucose and other blood chemistries.

We performed a diabetes education program again to standardize every patient's education for diabetes management and the method and frequency of self-monitoring of blood glucose (SMBG) according to glucose control. We provided overall orientation for all participants on diabetes management for 1 h, nutritional and exercise education for 2 h (including actual practice for 1 h), and had a question and answer session for 1 h.

In addition, the patients in the intervention group were taught to use the Internet-based system. Patients in both groups visited the outpatient clinic every 3 months for an interview conducted by their physician and provided a blood sample. The study period was from February 2002 to August 2004.

Glucose monitoring methods

Patients in the intervention group logged onto the Web site (www.biodang.com) at their convenience and uploaded their glucose levels (SMBG results) on a blood glucose board of the online chart. Additional information such as use of current medication, blood pressure, and weight were also uploaded. In addition, patients recorded in the memo box any changes in their lifestyle and any questions or detailed information that the patient wished to discuss, such as changes in diet, exercise, hypoglycemic events, and other factors that might influence the blood glucose level. The staff participating in the Internet-based system included three endocrinologists (a professor and two clinical instructors), a nurse, and a dietitian. The two clinical instructors logged onto the system daily and sent appropriate recommendations (based on the patients' uploaded blood glucose data) to each patient in the intervention group every 2 weeks. The recommendations were made according to the Staged Diabetes Management Guidelines in Korea (17). We did not adopt any other automated algorithms during the study. If there was any need to change the patient's medications or dosage, the clinical instructors referred the case to the professor. Any additional specific problems about self-management or lifestyle changes were referred to the nurse or dietitian.

In the offline system, patients visited the outpatient clinic every 3 months, where they had a face-to-face interview with their physician and provided a blood sample for follow-up laboratory testing. The telephone was not used for follow-

up, and, except for the tri-monthly clinic interviews, the patients communicated only via the Internet through their individualized electronic chart system.

The patients in the control group used a conventional note-keeping record system. Control patients were given our clinic's usual recommendations about medications, dosage, and lifestyle modification from the same endocrinologists who met with the intervention group.

A1C fluctuation index

In addition to calculating the mean A1C, we developed a new variable to investigate glucose stability during the study period because there could be difference in the risk of diabetes complications with the same mean A1C values (18). The SD value of A1C levels for each subject was named A1C fluctuation index (HFI), which represents the extent of change of A1C relative to the mean value during the study period. The HFI was calculated from A1C values taken after the initial 3-month follow-up point, since by then the levels already showed marked changes in the intervention group.

Statistical analysis

All results are expressed as means ± SD. The data were analyzed on an intent-to-treat basis with the last observation carried forward used for the end point. Student's *t* test was used to compare the two treatment groups (the Internet-based management system and routine outpatient management or control). A1C was treated as the major outcome variable. ANCOVA was used to control the effect of different basal values on the outcomes of interest and to compare changes from the basal to postintervention measurement between the two treatment groups. Repeated-measures ANOVA was used to determine whether A1C differed significantly over time or between the control and intervention groups. In the overall analysis, baseline measures with $P < 0.1$ between the two groups were used as covariants. For all tests, $P < 0.05$ was accepted as significant.

RESULTS— There was no significant difference between the two groups in comparison of clinical characteristics and mode of treatment for diabetes (Tables 1 and 2). After 30 months, there was a significant difference in the A1C and triglyceride levels between the control and intervention group (Table 2).

Seventy-one of the initial 80 subjects

Table 2—Laboratory follow-up data of subjects

Laboratory data	Baseline			15 months		30 months	
	Control	Intervention	<i>P</i>	Control	Intervention	Control	Intervention
FBG (mmol/l)	7.67 ± 2.08	8.07 ± 3.36	0.526	7.99 ± 1.85	8.96 ± 2.61	7.87 ± 1.83	8.51 ± 2.68
A1C (%)	7.5 ± 1.3	7.7 ± 1.5	0.457	7.4 ± 1.3	6.9 ± 1.1	7.4 ± 1.3	6.7 ± 0.9*
Total cholesterol (mmol/l)	4.8 ± 0.9	4.64 ± 0.8	0.403	4.27 ± 0.83	4.49 ± 0.72	4.49 ± 0.76	4.5 ± 0.67
Triglyceride (mmol/l)	1.68 ± 1.22	1.24 ± 0.8	0.062	1.5 ± 0.95	1.66 ± 1.29	1.28 ± 0.75	1.16 ± 0.73*
HDL cholesterol (mmol/l)	1.25 ± 0.38	1.29 ± 0.32	0.627	1.25 ± 0.32	1.22 ± 0.28	1.26 ± 0.34	1.37 ± 0.36
BUN (mg/dl)	15.2 ± 3.8	14.3 ± 3.4	0.285	15.7 ± 4.1	15.6 ± 3.4	16.2 ± 3.7	15.9 ± 4.5
Creatinine (mg/dl)	0.93 ± 0.18	0.89 ± 0.17	0.351	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2
AST (units/l)	23.9 ± 14.4	19.7 ± 15.4	0.123	23.0 ± 8.5	21.8 ± 11.9	22.5 ± 7.4	20.7 ± 7.6
ALT (units/l)	25.3 ± 14.5	22.5 ± 15.4	0.404	28.6 ± 13.9	24.4 ± 13.6	27.3 ± 10.8	25.2 ± 12.9
Na (mmol/l)	140.5 ± 2.6	140.3 ± 2.6	0.825	141.5 ± 3.4	140.8 ± 2.5	142.1 ± 4.1	140.6 ± 2.6
K (mmol/l)	4.18 ± 0.36	4.25 ± 0.40	0.455	4.3 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.4 ± 0.4

Data are mean ± SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FBG, fasting blood glucose.

(89%) completed the study. The overall drop-out rates were similar between groups: four subjects in the control group and five in the intervention group were withdrawn because they missed laboratory follow-up tests or did not visit the diabetes center more than three times during the study period.

About 50% (21 of 40) of subjects in the intervention group logged in to the system more than three times per week, ~30% (11 of 40) logged in less than twice per week on average, and ~20% (9 of 40) subjects used the system irregularly (two to three times per month).

An average of 5 min per patient was needed to interpret the uploaded information and send a message or reply. As a result, every 2 weeks, ~3–4 h for 40 patients in the intervention group were needed because the physicians sent messages to the patients at 2-week intervals.

The long-term effects of IBGMS on glycemic control

The basal A1C values were 7.5 ± 1.3 and 7.7 ± 1.5% in the control and intervention groups, respectively (*P* = 0.457). The mean A1C over the entire study period was significantly higher in the control (7.5 ± 1.0%) than in the intervention (6.9 ± 0.9%, *P* = 0.009) group (Fig. 1A, a). The mean A1C of subjects in the experimental group with a basal A1C of <7% during the whole study period was 6.2 ± 0.7%, which was significantly lower than that of the control group (6.9 ± 0.8%, *P* = 0.015) (Fig. 1A, b). In addition, there was also a significant difference in the mean A1C of subjects with a basal A1C ≥7% between the control and intervention groups (7.9 ± 1.0 vs

7.3 ± 0.7%, respectively; *P* = 0.023) (Fig. 1A, c).

Changes in A1C levels

For patients in the intervention group with a basal A1C ≥7%, the levels declined markedly during the first 3 months (Fig. 1C, a) and then continued to decrease at a slower rate. In contrast, A1C levels were irregular in the control group, although there was a generally modest reduction throughout the study. The patterns of change in both groups were significantly different (*P* = 0.022). For the control patients with a basal A1C <7%, A1C levels showed a characteristic “sine curve” bimodal response (Fig. 1C, b) with an initial decrease followed by a continuing increase after the first 6 months. By contrast, the A1C level of the intervention group remained stable and <7% during the entire study (control versus intervention group, *P* = 0.029).

The long-term effects of IBGMS on glucose stability

The HFI was significantly lower in the intervention group than in the control group (0.47 ± 0.23 vs. 0.78 ± 0.51, *P* = 0.001) (Fig. 1B, a). There was also a significant difference in HFI between both of the subgroups with a basal A1C <7% (0.84 ± 0.67 in the control group vs. 0.39 ± 0.26 in the intervention group, *P* = 0.03) (Fig. 1B, b). The HFI of the intervention subgroup with a basal A1C ≥7.0% was 0.51 ± 0.27, which was significantly lower than that of the control group (0.74 ± 0.40, *P* = 0.015) (Fig. 1B, c).

Role of self-monitoring of blood glucose in changes of A1C and HFI

Participants using insulin or oral agents were instructed to check their blood glucose levels using self-monitoring of blood glucose (SMBG) at least once a day and those with lifestyle modification at least twice a week. Each treatment group was divided into a good compliance (GC) and a poor compliance (PC) subgroup. Patients in the GC group were defined as those who complied with SMBG at a frequency of ≥80% compared with the initially recommended rate. The mean monthly frequency of applying SMBG was 22 ± 19 in the control group and 34 ± 28 in the intervention group (*P* = 0.024). The basal A1C level showed no significant difference between the GC and PC subgroups in both control and intervention groups. There was also no significant difference in mean A1C between GC and PC subgroups, although the mean A1C level of GC subgroup showed a lower tendency compared with that of the PC subgroup (Fig. 2A).

The HFI value in the GC and PC subgroups of the intervention group did not differ significantly. However, in the subjects with a basal A1C ≥7% in the control group, the HFI was significantly lower in the GC subgroup than in the PC subgroup (0.43 ± 0.20 vs. 0.93 ± 0.37, respectively; *P* < 0.01) (Fig. 2B).

In the A1C follow-up curve of the intervention group with a basal A1C ≥7%, A1C levels after the 15-month point showed a difference between the GC and PC subgroups. The curve of the PC subgroup started to increase gradually, while that of the GC subgroup decreased continuously (Fig. 2C, a). The mean A1C of

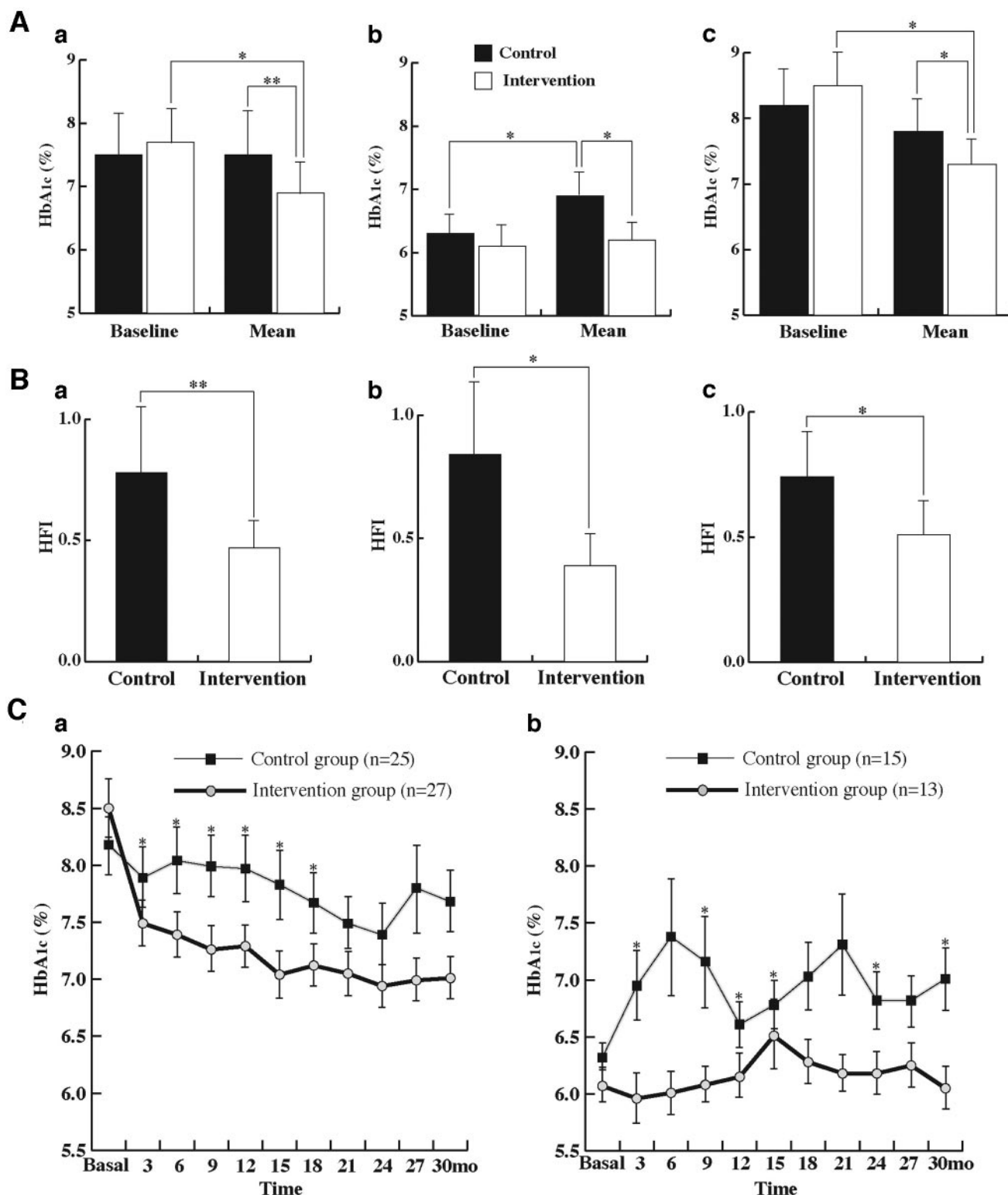


Figure 1—The effects of intervention (IBGMS) on changes of A1C and glucose stability. A: Baseline A1C and mean A1C during the study 30-month period. a: All subjects, control (n = 40) vs. intervention (n = 40). b: Subjects with a basal A1C <7%, control (n = 15) vs. intervention (n = 13). c: Subjects with a basal A1C ≥7%, control (n = 25) vs. intervention (n = 27). B: Difference of HFI between the control and intervention groups. a: All subjects. b: Subjects with a basal A1C <7%. c: Subjects with a basal A1C ≥7%. C: Fluctuating line of A1C for the 30 months. a: Subjects with a basal A1C ≥7%. b: Subjects with a basal A1C <7%. At each follow-up point, ≥90% of patients took the test. *P < 0.05; **P < 0.01.

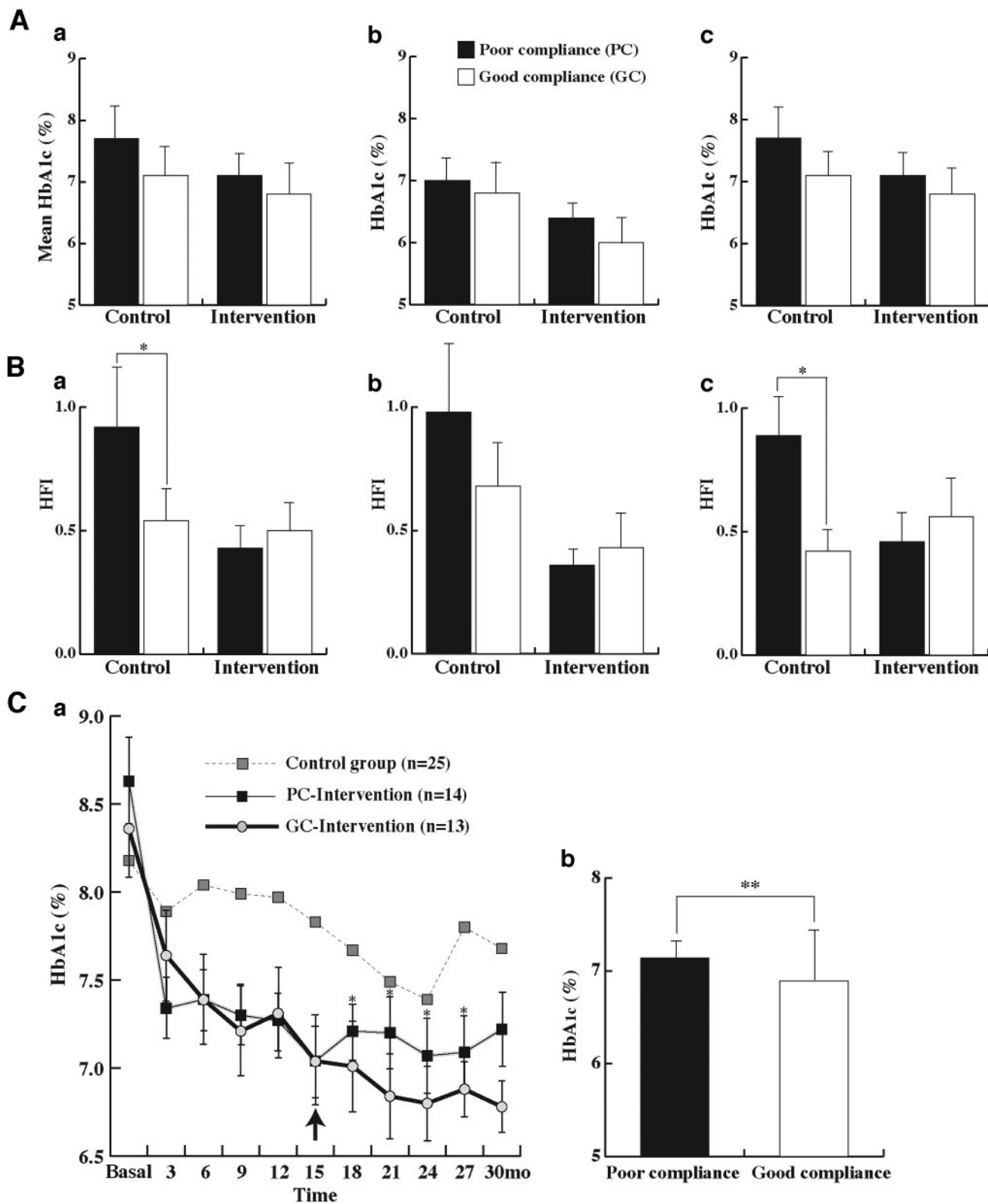


Figure 2—Role of SMBG in A1C change and glucose stability. A: Difference of the mean A1C between PC and GC subgroups. a: All subjects. b: Subjects with a basal A1C <7%. c: Subjects with a basal A1C ≥7%. B: Difference of HFI between PC and GC subgroups. a: All subjects. b: Subjects with a basal A1C <7%. c: Subjects with a basal A1C ≥7%. A, a and B, a: Number of subjects of PC and GC control was 25 vs. 15 and that of PC and GC intervention was 19 vs. 21. A, b and B, b: Number of subjects was 8 vs. 7 for the control group and 5 vs. 8 for the intervention group. A, c and B, c: Number of subjects was 17 vs. 8 for the control group and 14 vs. 13 for the intervention group. C, a: Fluctuating line of A1C in subjects with a basal A1C ≥7%. C, b: Difference of mean A1C of the PC and GC subgroups in the intervention group from 15 months after the intervention to the end of study. At each follow-up point, ≥90% of the patients carried out the test. *Mean P < 0.05; **P < 0.01.

Table 3—Staff recommendations and patient reports through the IBGMS

Recommendations provided by staff	
Lifestyle modification	201 (12.6)
Drug modification*	192 (12.1)
Encouragements	661 (41.7)
Problem assessment and counseling	532 (33.5)
Total cases	1,586
Reports recorded in memoranda by patients	
SMBG related	76 (15.0)
Changes in lifestyle	213 (42.0)
Drug related	124 (24.5)
Hypoglycemic events	32 (6.3)
Any other factors that might affect glucose level†	31 (6.1)
Others	30 (5.9)
Total cases	507

Data are n (%). *Mostly short-term changes, for approximately <1 week. †Symptoms such as diarrhea, pain, cough, ingestion of other drugs, admission to hospital, or overseas travel.

the GC subgroup during the period from 15 months to the end of study was lower than that of the PC subgroup (6.89 ± 1.09 vs. $7.14 \pm 0.08\%$, respectively; $P < 0.01$) (Fig. 2C, b).

The contents of bidirectional communications through the IBGMS

The total occasions of drug modification in the outpatient clinic was 187 times (mean 5.5 ± 4.7 times/person) in the control subjects and 150 times (4.7 ± 2.9 times/person) in those of the intervention group, with no significant differences between the two groups.

Table 3 shows the contents of the communication between the staff and patients through the IBGMS. The support staff made 1,586 recommendations during the study period (45.3 per person), and 507 reports were recorded in memoranda by the patients (14.5 per person). Of the recommendations recorded by doctors, most (661 of 1,586 [41.7%]) were in the form of “encouragement” and “problem assessment and counseling” was the second most frequent (532 of 1,586 [33.5%]) comment. Contrary to our expectation, the frequency of “drug modification” was lowest (192 of 1,586 [12.1%]). Most of the reports recorded in the memorandum box by patients concerned information about “changes in lifestyle” (213 of 507 [42%]). “Hypoglycemic events” was the subject of 6.3% (32 of 507) of the reports.

CONCLUSIONS— We have demonstrated the long-term effectiveness of IBGMS, which is characterized by a bidirectional system through which both the patient and physician can interactively communicate by close monitoring and by a data-based management system that includes charts of IBGMS. As a result, IBGMS could provide seasonal advice and feedback, continuous motivation for glucose control, frequent encouragement, problem assessment, and individualized education about diet and exercise as well as drug modification. Thus, IBGMS not only provides an increase of contact with patients but also many other additive effects.

In the study, we focused on type 2 diabetes rather than type 1 diabetes (19,20), and this study has the longest follow-up period and includes well-controlled patients as well as poorly controlled patients, while the longest study period in previous reports had a 1-year follow-up period and included only poorly controlled subjects with type 2 diabetes (21). We observed improvement of HFI and reduction of glucose.

The mean A1C value during the study decreased significantly in the intervention group compared with the control group. There were more subjects with a mean A1C <6.5% in the intervention (37%) than in the control (17%) group.

Regarding changes in A1C levels, subjects with a basal A1C <7% showed a bimodal curve of 6.3–7.4% in the control group and 6.1–6.5% in the intervention group. These data indicate that even in the subjects who had strictly controlled blood glucose, there were some variations and fluctuations in blood glucose control. However, when the IBGMS was applied, it made the fluctuations in lesser degrees. Moreover, the HFI value, which reflects fluctuations in A1C levels, was significantly lower in the intervention group than in the control group. In addition to glycemic control, large fluctuation of plasma glucose is regarded as a risk factor for developing long-term complications (22–27). Therefore, the lesser fluctuations of glucose levels would be expected to better prevent long-term diabetes complications. Although we did not evaluate the complications of the subjects, IBGMS had more benefits in glucose control from both the quantitative aspect (mean A1C levels) and the qualitative aspect (stability in blood glucose level).

Through IBGMS, physician’s contact time was relatively reduced compared

with face-to-face interview in the office, probably because the physician can analyze well-arranged data and answer immediately. Furthermore, patients have to spend at least several hours to visit and contact their physician in the office. Thus, we expect that physicians could monitor patients’ glucose control data more efficiently within a short time through the IBGMS, and IBGMS could also save the patients’ time by minimizing the frequency of hospital visits.

If SMBG has been recommended to improve glycemic control and better self-management, studies of the effect of SMBG on people with type 2 diabetes have produced mixed results (28–31). In this study, the frequency of SMBG may not have been the main factor for glucose control and stability in the subjects receiving intervention. Thus, the responses of the support staff to patients at the appropriate time, plus continuous motivation, may be more important than glucose self-measurement per se. The frequency of SMBG wasn’t related to the mean A1C levels, but high frequency of SMBG showed some beneficial effects on glucose stability in control (Fig. 2B, a and c). The A1C follow-up curve of the GC subgroup after 15 months continuously maintained well compared with that of the PC subgroup in the intervention group. Therefore, SMBG in diabetic patients is important not only in achieving lesser fluctuations of glucose levels but also in long-term maintenance of appropriate A1C levels, even in the intervention group.

In conclusion, we have confirmed the long-term effectiveness of the IBGMS system on glucose stability and A1C reduction. We expect that the IBGMS will contribute to reducing complications and improving the quality of life for patients with diabetes.

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