Immediate Feedback of HbA$_{1c}$ Levels Improves Glycemic Control in Type 1 and Insulin-Treated Type 2 Diabetic Patients

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OBJECTIVE — Accurate and reliable HbA$_{1c}$ results can be obtained at the time of the office visit by using benchtop analyzers. We tested the hypothesis that immediately available HbA$_{1c}$ results could improve glycemic control by changing physician or patient behavior or both.

RESEARCH DESIGN AND METHODS — A randomized controlled trial was conducted in 201 type 1 and insulin-treated type 2 diabetic patients attending an academic diabetes center. HbA$_{1c}$ levels, changes in insulin therapy, and use of health care resources were assessed during a 12-month follow-up period.

RESULTS — HbA$_{1c}$ levels decreased significantly at 6 and 12 months in the immediate assay group (-0.57 ± 1.44 and $-0.40 \pm 1.65\%$, respectively; $P < 0.01$) but did not change in the control group (-0.11 ± 0.79 and $-0.19 \pm 1.16\%$, respectively; NS). The changes were similar for both type 1 and type 2 diabetic patients. There were no differences in the rates of hypoglycemic events or use of health care resources.

CONCLUSIONS — In the setting of a controlled randomized trial, the immediate feedback of HbA$_{1c}$ results at the time of patient encounters resulted in a significant improvement of glycemic control at 6-month follow-up and persisted for the 12-month study. The introduction of this assay was positively received by both patients and physicians.

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The glycosylated hemoglobin assay provides the most objective and reliable information about long-term glucose control in diabetic patients (1,2). It is widely used to guide hypoglycemic therapy and has been demonstrated to be effective in identifying patients with unacceptably poor glycemic control and to facilitate their improvement (3). While it does not reveal details about daily glycemic excursion, the glycosylated hemoglobin assay can be useful to verify the accuracy of self-glucose monitoring and provides essential information for patients who do not self-monitor their glucose. For these reasons, routine determinations of glycosylated hemoglobin values have become an essential component of the standard of care for diabetic patients (4). Clinical trials such as the Diabetes Control and Complications Trial (5) and the U.K. Prospective Diabetes Study (6) have established specific HbA$_{1c}$ goals that result in substantial reductions in long-term complications.

Several assays to measure glycosylated hemoglobin are currently available, with high-performance liquid chromatography (HPLC) still considered the reference method (7,8). However, most of these methods are time-consuming and technically demanding, with the results of the assay not being available at the time of the patient encounter. Thus, an important element in the clinical decision-making process is not available at the time of the office visit. The delay in assay result is inefficient, requiring the health care provider to communicate the result and attendant changes in therapy to the patient after the visit. Moreover, delayed patient feedback could lead to decreased patient compliance and could delay adjustment of hypoglycemic regimens.

Immediately available ("point of service") HbA$_{1c}$ results can now be obtained with a benchtop analyzer (DCA 2000; Bayer, Elkhart, IN) that has been shown to provide accurate and reliable results (9–14). We performed a randomized controlled trial to test the hypothesis that HbA$_{1c}$ results available at the time of physician encounter could improve glucose control by changing physician and/or patient behavior.

RESEARCH DESIGN AND METHODS — The study population consisted of type 1 and insulin-treated type 2 diabetic patients attending the Massachusetts General Hospital Diabetes Center. We studied 201 consecutive patients who gave informed consent and fulfilled the following inclusion criteria: age >18 years, type 1 or insulin-treated type 2 diabetes for >1 year, diabetes care provided by the Diabetes Center, and knowledge of the English language. Less than 10% of eligible patients declined to participate in the study. Patients were randomly assigned to one of two groups: one group had HbA$_{1c}$ levels determined at the time of the office visit with the benchtop analyzer so that results of the HbA$_{1c}$ test were available to the individual physicians at the beginning of the visit (immediate assay group), and the other had HbA$_{1c}$ levels measured by the diabetes laboratory as per usual clinical practice (control group).

The patients were treated by staff physicians and endocrinology fellows; the physicians were aware of the nature of the study (clinical evaluation of immediate HbA$_{1c}$ assay) but were masked to the specific outcomes collected (e.g., frequency of visits, changes in therapy, contacts with patients) to avoid bias in the treatment of the patients.
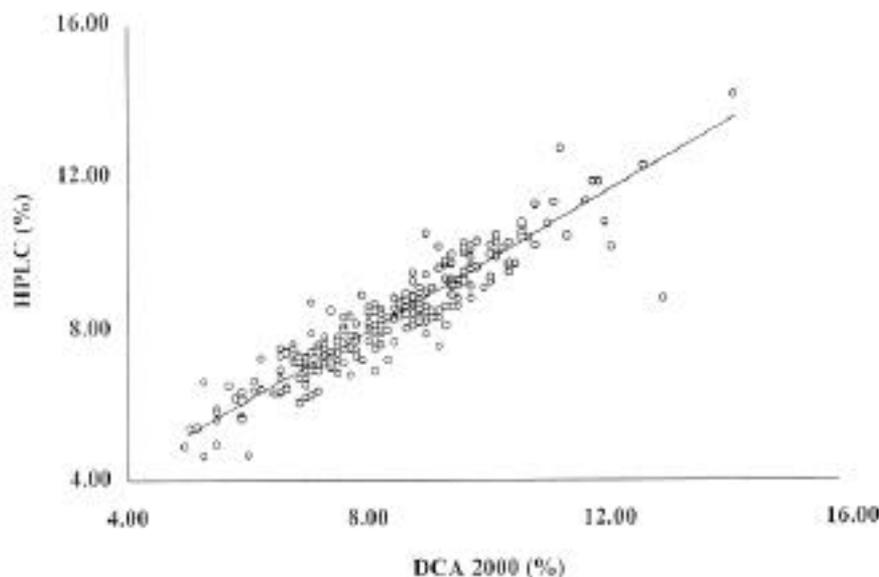
Figure 1—*Correlation of HbA$_{1c}$ values (%) performed by the HPLC and DCA 2000 assays. Correlation coefficient* (r) = 0.9239, P < 0.001.

Changes in insulin dosage and frequency of follow-up were determined by the clinicians.

The primary outcome was the change in HbA$_{1c}$ levels, as determined by the HPLC assay in all patients, over the 1-year study period. The secondary outcomes included changes in insulin therapy, hypoglycemic episodes, and use of health care resources as determined by patient questionnaires and chart reviews. Patients were asked to fill out a short questionnaire at each office visit. The questionnaire was designed to obtain information about insulin regimen, any contacts that patients had with their health care providers (by either telephone or mail), episodes of severe hypoglycemia (defined as requiring assistance from another person or visit to hospital), visits to emergency rooms, or hospital admission. At study end, charts were reviewed by one of us (E.L.) to confirm the above information. The number of office visits and data on lipids were also captured at study end by way of chart review.

In a preliminary phase of the study, the performance of the bench-top analyzer was compared with the HPLC assay currently in use in the diabetes laboratory at Massachusetts General Hospital. The Pearson's correlation coefficient between the two assays was 0.9239 ($n = 264$) (Fig. 1), and the mean difference (benchtop HPLC) was 0.071 ± 0.582. The HPLC assay has been described previously (1) and has inter- and intra-assay coefficients of variation (CVs) <2.5% for high and low standards. The interassay CV

for the benchtop measurements was 2.1%, and the intra-assay CV was 2.0%.

Statistical analysis was performed by two-tailed t test (paired when appropriate) or by Wilcoxon rank-sum test for continuous variables (reported as mean ± SD), and for nominal variables by the χ^2 test. Data were analyzed with the statistics data management program STATA (Computing Resource Center, Santa Monica, CA).

RESULTS — The immediate assay and control groups had similar baseline characteristics, including HbA$_{1c}$ (8.67 ± 1.79 vs. 8.49 ± 1.59, respectively; NS), insulin dose, and number of injections per day (Table 1). The mean duration of follow-up was identical for the two groups (immediate assay, 12.8 ± 1.8 months; control, 12.8 ± 1.6 months). There were 37 patients (18%)

who did not complete the study: 14 in the immediate assay group and 23 in the control group (NS). Of those 37 patients, 3 died (1 in the immediate assay group and 2 in the control group), 1 in the immediate assay group refused further participation in the study, 6 switched their care to other physicians, 7 were lost to follow-up, and 20 did not have any HbA$_{1c}$ determinations within a 6-month period of study end. The patients who did not complete the study had higher baseline HbA$_{1c}$ levels than the patients who completed the 1-year follow-up (9.20 ± 1.51 vs. 8.44 ± 1.70; $P = 0.0125$) but otherwise had similar baseline characteristics. The remaining analysis was performed on the 164 patients who completed the study.

After approximately 6 and 12 months, HbA$_{1c}$ (measured by HPLC) decreased significantly in the immediate assay group but did not change significantly in the control group (Fig. 2). HbA$_{1c}$ levels decreased by 0.57 ± 1.44% ($P = 0.001$) at 6 months and 0.40 ± 0.65% ($P = 0.013$) at 12 months in the immediate assay group. In the control group, HbA$_{1c}$ levels decreased by 0.11 ± 0.79% (NS) at 6 months and 0.19 ± 1.16% (NS) at 12 months. The difference between the two groups was statistically significant at 6 months ($P = 0.029$) but not at study end ($P = 0.346$). When the 6-month data were analyzed including patients who did not complete the study (intention to treat mode), the difference between the two groups remained statistically significant ($P = 0.022$).

The changes in HbA$_{1c}$ levels were similar for both type 1 and type 2 diabetic patients. At 6 months, HbA$_{1c}$ levels decreased by 0.29 ± 0.95% in type 1 and 0.84 ± 1.86% in type 2 diabetic patients in the immediate assay group; in the control group, they decreased by 0.07 ± 0.81 and

Table 1—*Baseline characteristics*

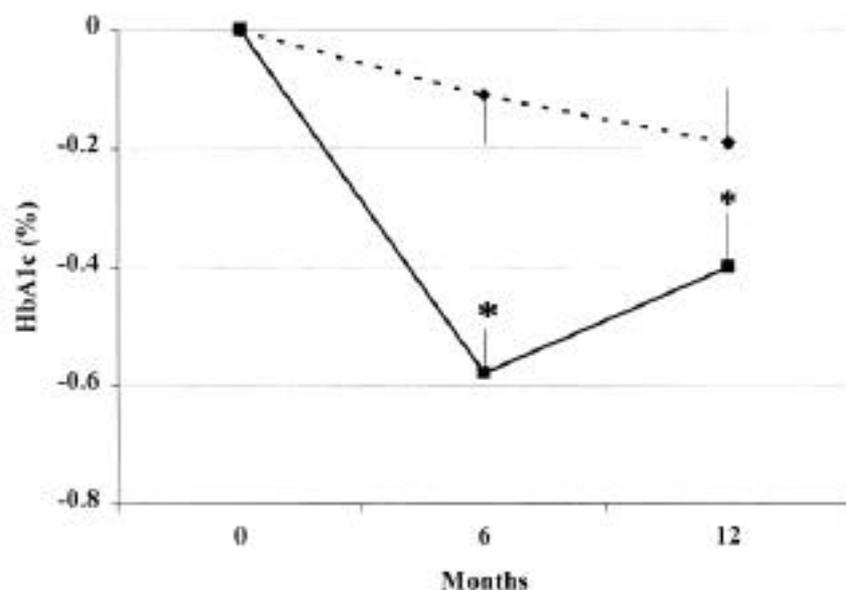|	Immediate assay	Control	Significance (P)
n	100	101	—
Age (years)	49 ± 16	49 ± 16	0.9147
Sex (% male)	48	58	0.1168
Diabetes (% type 1)	56	56	0.8851
HbA$_{1c}$ (%)	8.67 ± 1.79	8.49 ± 1.59	0.4518
Insulin dose (U/day)	51.8 ± 28.8	53.9 ± 34.2	0.9741
Insulin injections (number/day)	2.21 ± 0.98	2.33 ± 1.00	0.3756
Triglycerides (mg/dl)	177 ± 206	116 ± 66	0.2874
Cholesterol (mg/dl)	205 ± 39	194 ± 42	0.1173

Data are means ± SD.

Figure 2—*Changes in HbA$_{1c}$ levels (%) from baseline at 6- and 12-month follow-up in the Control (◆) and immediate assay (■) groups. Data are presented as means ± SEM. *P < 0.05 vs. baseline.*

0.16 ± 2.32 for type 1 and type 2 diabetic patients, respectively. At study end, HbA$_{1c}$ levels decreased by 0.34 ± 1.06% in type 1 and 0.49 ± 2.25% in type 2 diabetic patients in the immediate assay group. In the control group, HbA$_{1c}$ levels decreased by 0.24 ± 1.03 and 0.13 ± 1.32% for type 1 and type 2 diabetic patients, respectively.

The mean daily insulin dose increased from 55.3 ± 36.6 to 59.9 ± 42.6 U/day in the control group ($P = 0.012$) but was unchanged during the 1-year study in the immediate assay group (baseline 49.9 ± 27.5 to 50.7 ± 26.9 U/day at study end; NS). The mean number of daily insulin injections was unchanged over the course of the study in the control group (from 2.42 to 2.45 injections/day; NS) and increased in the immediate assay group (from 2.29 ± 0.97 to 2.45 ± 0.95; $P = 0.001$). Changes in insulin regimens (either dose or frequency) occurred in 83% of patients in the control group and 69% of the immediate assay group ($P = 0.028$); these changes were initiated by the physician in most cases (66% in the control group versus 74% in the immediate assay group; NS), but were self-initiated in 34% of the control patients and 26% of the immediate assay patients (NS).

There was no difference in the use of health care resources between the two groups (Table 2). Forty-nine patients (30%) reported at least one episode of severe hypoglycemia during the study, with no differences between patients in the immediate assay group (30%) and the con-

trol group (29%). There were 98 episodes of severe hypoglycemia in the immediate assay group with 17 visits to the emergency room and 111 episodes in the control group with 14 visits to the emergency room (NS). The mean number of severe hypoglycemic episodes was 1.14 ± 2.84/year (median 0, interquartile range 1–0) in the immediate assay group and 1.42 ± 4.27/year (median 0, interquartile range 1–0) in the control group (NS), while the number of visits to the emergency room was 0.35 ± 0.66/year (median 0, interquartile range 0–0) in the immediate assay group versus 0.37 ± 0.64/year (median 0, interquartile range 0–0) in the control

group (NS). The number of severe hypoglycemia episodes was 1.95 ± 4.57/year (median 0, interquartile range 1–0) in type 1 diabetic patients versus 0.40 ± 1.09/year (median 0, interquartile range 0–0) in type 2 diabetic patients ($P < 0.001$). Six patients (3%) were hospitalized (for any reason) during the study, two in the immediate assay group and four in the control group (NS). The mean number of visits to the Diabetes Center per year was 4.72 ± 1.83 in the immediate assay group and 4.98 ± 1.93 in the control group (NS). The number of HbA$_{1c}$ determinations during the study period was 3.69 ± 0.90 in the immediate assay group and 3.61 ± 0.92 in the control group (NS).

The availability of immediate HbA$_{1c}$ values at the time of office visit did not decrease significantly the number of contacts (by either letter or telephone) that patients had with their health care providers between office visits. Overall, 91% of the patients were contacted at least once by their health care providers (physician or nurse) between office visits, usually to report results of laboratory tests. The mean number of contacts per year was 2.44 ± 1.28 in the immediate assay group versus 2.73 ± 1.84 in the control group (NS), and there was no difference in the breakdown between letters or telephone calls from physicians or nurses (Table 2). However, the pattern of contacts varied remarkably between individual physicians and their patients, and one of the six staff physicians showed a significant decrease in letters to patients (2.63 ± 0.92 in the control group versus 1.54 ± 1.21 in the immediate assay group, $P < 0.05$).

Table 2—*Use of health care resources*

	Immediate assay	Control	Significance (P)
n	86	78	—
Percent of patients with changes in insulin regimen	69	83	0.028
Physician initiated	74	66	0.576
Patient initiated	26	34	0.076
Percent of patients with:			
Severe hypoglycemia*	30	29	0.917
Visits to emergency room	15	14	0.464
Outpatient visits (number/year)	4.72 ± 1.83	4.98 ± 1.93	0.377
Contact with patients (number/year)	2.44 ± 1.28	2.73 ± 1.84	0.239
Letters from doctor	1.58 ± 1.21	1.41 ± 1.32	0.39
Phone calls from doctor	0.48 ± 0.92	0.69 ± 1.25	0.219
Contacts from nurse	0.36 ± 1.04	0.60 ± 1.27	0.1

Data are means ± SD. *Assessed by questionnaire at each visit.

CONCLUSIONS — The purpose of this randomized clinical trial was to determine whether availability of HbA_{1c} results at the time of an office visit would lead to improved glycemic control. The immediate feedback provided by the benchtop analyzer resulted in a significant decrease in HbA_{1c} at 6- and 12-month follow-up, while HbA_{1c} levels did not change in the control group. These results occurred in both type 1 and insulin-treated type 2 diabetic patients, the patient populations in which frequent changes in insulin therapy are mandated to achieve near-normoglycemia. Because of the nature of the intervention, the randomized trial could not be effectively double-blind; however, the physicians providing clinical care were only aware of the goal of "clinical evaluation of the DCA 2000 analyzer" and did not know that their behavior, as well as patient compliance, was being evaluated. The results of the current study are in general agreement with those of a 6-month study by Marrero et al. reported as an abstract (15) that showed improved glycemic control in patients whose providers were selected to receive immediate HbA_{1c} results. The important role of the glycohemoglobin assay in facilitating improved glycemic control, independent of the timing of the result reporting, has been demonstrated previously (3).

The patient population studied reflected the overall population of diabetic patients followed in the Massachusetts General Hospital Diabetes Center: type 1 diabetic patients with mean age of 40 ± 12 years, baseline HbA_{1c} of 8.21 ± 1.49, and daily insulin dose of 45 ± 18 U, and type 2 diabetic patients with a mean age of 60 ± 11 years, baseline HbA_{1c} of 8.72 ± 1.91, and daily insulin dose of 61 ± 42 U. Moreover, the modest exclusion criteria for the trial and the >90% enrollment rate of patients asked to participate in this study underscore the generalizability of the findings of this clinical trial to the insulin-treated diabetic population. Measurement of HbA_{1c} occurred on average 3.65 ± 0.91 times/year, and the number of office encounters per year was 4.85 ± 1.88/year, values that are quite similar to those observed in a random sample of diabetic patients followed in the Diabetes Center (16), suggesting that the care provided to this patient population was reflective of the overall care provided by the six staff physicians and three clinical fellows that are part of the Diabetes Center.

No specific changes in behavior were identified as being responsible for the improved glycemic control in the immediate assay group. Total insulin dose did not change, although a small, but statistically significant, increase in the frequency of daily insulin injections was detected. The patients in the immediate assay group changed insulin regimens less frequently than patients in the control group (Table 2), and the improved glycemic control they experienced suggests the possibility that immediate feedback of HbA_{1c} results was more likely to induce clinically appropriate adjustments of insulin regimens.

The improvement in glycemic control was not accompanied by an increase in severe hypoglycemic episodes, visits to emergency rooms, or increased use of health care resources. The number of phone and letter contacts by the health care providers to diabetic patients did not change significantly, contrary to our expectations, in the immediate assay group. The failure to decrease patient contacts may be due to the need to report other laboratory data (e.g., lipid values). Contacts from physician and nurses were assessed by both patient questionnaire and chart review at the end of the study period, and it is unlikely that they were grossly underestimated. Moreover, it is unlikely that such events would have been estimated differently in the experimental and control groups. While no cost savings were realized from different frequency of follow-up or use of medical resources between the two groups, the cost savings associated with a 0.5% decrease in HbA_{1c} have been established (17,18).

In summary, the benchtop, point-of-service analyzer provided reliable and accurate determinations of HbA_{1c} levels, in accordance with previously reported studies (9–14). The immediate feedback of HbA_{1c} results available at the time of patient encounters resulted in a significant improvement of glycemic control at 6 months and persisted for the entire 12-month controlled randomized trial. The introduction of this methodology was positively received by both patients and physicians.

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