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Randomized Trial of Fructosamine Home Monitoring in Patients with Diabetes

CONTEXT. Recognition of the importance of glycemic control in type 2 diabetes has generated interest in developing ways to improve such control. Levels of fructosamine, 1-amino-1-deoxyfructose, are highly correlated with those of hemoglobin A_{1c} (HbA_{1c}) and can be monitored in the home.

DESIGN. Randomized trial.

PARTICIPANTS. 140 adult patients with HbA_{1c} values of 8% or greater were recruited to the trial through referral from physicians and a direct mailing to potentially eligible persons.

INTERVENTION. Weekly home fructosamine monitoring in addition to daily glucose monitoring. Control patients monitored daily glucose only. Both groups of patients were contacted regularly by telephone and were given the same instructions on diet and exercise.

OUTCOME. Measures of glycemic control 3 and 6 months after randomization.

RESULTS. No significant difference was found between the two groups in the mean absolute decrease of HbA_{1c} levels at 3 months (0.5% in the fructosamine group vs. 0.8% in the control group; $P > 0.2$), and the difference favored the control group at 6 months (0.7% fructosamine vs. 1.2% control; $P = 0.04$). Both groups had a statistically significant improvement in glycemic control.

CONCLUSIONS. The addition of home fructosamine monitoring to routine glucose monitoring did not improve glycemic control.

The Diabetes Control and Complications Trials (DCCT) showed that better glycemic control slows the development of neuropathy, nephropathy, and retinopathy in patients with type 1 diabetes.^{1,2} The importance of glycemic control in patients with type 2 diabetes was established in the United Kingdom Prospective Diabetes Study (UKPDS), which randomized patients who were recently diagnosed with type 2 diabetes to intensive treatment with sulfonylureas (chlorpropamide, glibenclamide, or glipizide) or insulin, or to conventional treatment beginning with diet.³ After 10 years of follow-up, when an 11% reduction in median hemoglobin A_{1c} (HbA_{1c}) levels was observed in the intensive-care group (HbA_{1c} levels 7.0% vs. 7.9% in the conventional-treatment group), the risk for microvascular complications in the intensive-care group was 25% lower. The Kumamoto Study, a small, randomized trial in insulin-dependent type 2 patients⁴ also found statistically significant reductions in the occurrence and progression of retinopathy, neuropathy, and microalbuminuria with intensive (multiple daily insulin injections) versus conventional insulin therapy during 6 years of follow-up.

Recognition of the importance of glycemic control in patients with type 2 diabetes has generated interest in developing effective and cost-effective strategies to

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improve such control. Most strategies to improve glycemic control include patient education and active involvement of the patient in self-care activities, which almost always include home monitoring of glucose.

The optimal frequency of home monitoring of glucose in type 2 diabetes is not known. The possibility that information on whether long-term glycemic control reflecting a long interval might help improve the

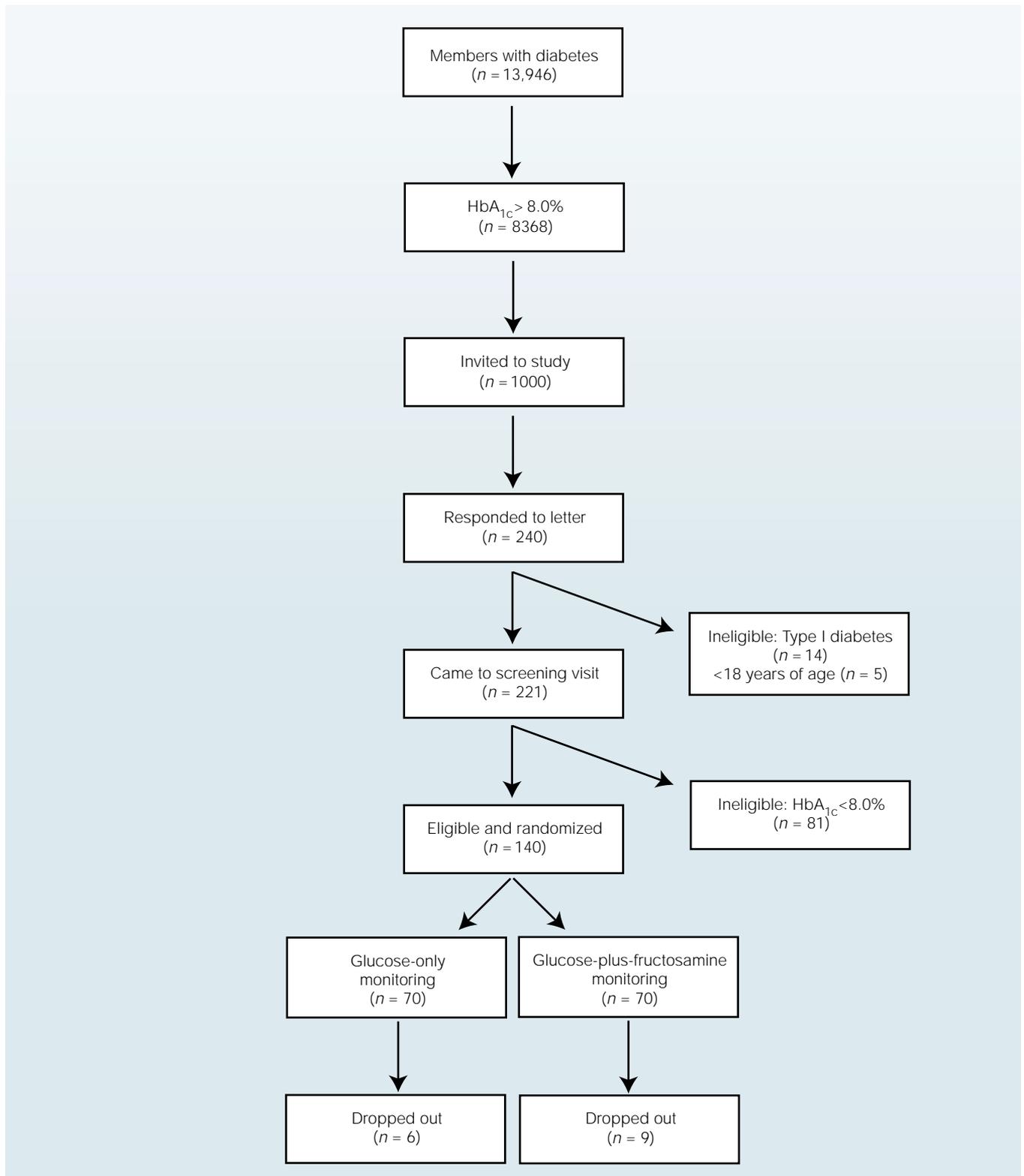


FIGURE 1. Flow diagram of patient recruitment and follow-up. HbA_{1c} = hemoglobin A_{1c}.

ability of patients to self-manage diabetes has not been studied because meters that allow such monitoring have not been available. Levels of fructosamine, 1-amino-1-deoxyfructose, are strongly correlated (0.79) with those of HbA_{1c}.⁵ Measuring fructosamine has been used as an alternative to measuring HbA_{1c} for assessment of glycemic control because it is technically simpler and often less costly. Fructosamine values reflect glycemic control over a shorter term than those of HbA_{1c} (2 to 4 weeks vs. 6 to 12 weeks). A device approved by the U.S. Food and Drug Administration for self-monitoring of fructosamine is available commercially. This randomized trial was designed to determine whether the addition of home monitoring of long-term glycemic control using fructosamine would improve glycemic control better than conventional home monitoring based only on glucose in patients with type 2 diabetes.

Methods

Participants

Patients 18 years of age or older were eligible for the trial if they had an HbA_{1c} result of 8% or greater, were not pregnant, were free of illnesses that might affect glucose control (infection, malignant conditions, renal failure, severe dyslipidemia), and were able to self-monitor glucose and fructosamine. Potentially eligible patients were identified from records of the Diabetes Care Clinic and through referrals from primary care physicians. In addition, patients known to have at least one recent HbA_{1c} value of 8% or greater selected at random from among all patients with such values were sent a letter describing the study and were given a phone number to call for more information.

Patients interested in the study after having the study procedures explained to them were asked to come to a screening visit. During this visit, the study was described in more detail and informed consent was obtained. A screening HbA_{1c} measurement was obtained.

Consenting patients with a screening HbA_{1c} of 8% or greater returned the following week (baseline visit) and were randomly assigned to at least daily home monitoring of glucose only or to daily glucose monitoring plus weekly monitoring of fructosamine. At this time, both groups received instructions on glucose and fructosamine monitoring, and baseline HbA_{1c} and fructosamine levels were measured. **Figure 1** outlines the flow of patients into the study.

Intervention and Follow-up

Patients assigned to the glucose-only monitoring group were instructed to perform at least one, but no more

than four, standard glucose self-tests daily. Patients assigned to the glucose-plus-fructosamine monitoring group were similarly instructed and were requested to perform a fructosamine self-test once a week.

To assess compliance, patients in both groups were contacted by telephone 2 and 4 weeks after randomization and monthly thereafter. Patients were also asked to keep a record of the number of glucose strips used. In addition, both groups were given the same instructions on diet and exercise.

At the end of 3 months, patients were asked to return to the clinic to receive an additional 3-month supply of strips. The patients were also asked to return the unused strips for counting. Follow-up HbA_{1c} and fructosamine measurements were taken. Patients continued to receive monthly telephone counseling for the remaining 3 months and were asked to return for a final visit at 6 months. Final HbA_{1c} and fructosamine measurements were obtained, and the unused strips were counted.

Statistical Analysis

A sample size of 60 patients per group was calculated to be required to detect a difference in reduction of HbA_{1c} of 0.8% at a 5% significance level (two-tailed test) with a power of 0.80. In estimating sample size, it was assumed that HbA_{1c} would decrease by 0.2% in the glucose-only monitoring group. To compensate for an expected dropout rate of 15% and thus to ensure an adequate sample size, 140 patients (70 in each group) were enrolled.

Baseline characteristics were compared using the chi-square test and the two-sample *t*-test. The *t*-test was used to compare the difference in the change HbA_{1c} and fructosamine measurements between the glucose-only and glucose-plus-fructosamine groups at 3 months and 6 months. The proportion of patients achieving good glycemic control (fructosamine <320 mg/dL or HbA_{1c} < 8.0%) in each group was compared using the chi-square test at 3 and 6 months. The statistical significance of the within-group changes in HbA_{1c} and fructosamine compared with baseline were assessed using the paired *t*-test.

All interval-scaled variables were tested for normality using the Shapiro-Wilk test. If the variable did not have a normal distribution, then the signed-rank test was used instead of the one-sample *t*-test. The two sample *t*-test was replaced by the Mann-Whitney test if the variable was not normally distributed. Results were considered statistically significant when the two-sided *P* value was <0.05.

This study was reviewed and approved by the Kaiser Permanente Institutional Review Board. All patients consented in writing to participate.

TABLE 1

Patient Demographics and Baseline Values of Hemoglobin A_{1c} and Fructosamine

VARIABLE	GLUCOSE PLUS FRUCTOSAMINE (n=70)	GLUCOSE ONLY (n=70)	P VALUE
Age, yr (mean ± SD)	60.0 (11.0)	59.9 (10.0)	>0.2
Male, n	39	39	
Hemoglobin A _{1c} , % (mean ± SD)	9.1 (1.3)	9.2 (1.0)	>0.2
Fructosamine, mg/dL (mean ± SD)	362 (50)	362 (55)	>0.2

Results

A total of 140 patients were recruited to the study; 70 were assigned to glucose-only monitoring and 70 to glucose-plus-fructosamine monitoring. There were no statistically significant differences in patient characteristics between the two groups at baseline (Table 1). After 6 months, six patients in the glucose-only monitoring group and nine patients in the glucose-plus-fructosamine monitoring group dropped out. All patients, including those who dropped out after 3 months, were included in the analysis if data were available.

Figure 2 shows fructosamine and HbA_{1c} values in the two monitoring groups at baseline and 3 and 6 months after baseline. The mean decrease in HbA_{1c} at 3 months between the glucose-only (0.8%) and the glucose-plus-fructosamine monitoring groups (0.5%; $P>0.2$) was not statistically significant. At 6 months, the mean decrease in HbA_{1c} in the glucose-only monitoring group was 1.2%, whereas it was 0.7% in the glucose-plus-fructosamine monitoring group ($P=0.04$). In addition, there was not a statistically significant change in mean fructosamine level between the two groups at either 3 or 6 months.

Compared with baseline, both groups had statistically significant decreases in HbA_{1c} and fructosamine levels at both 3 months and 6 months (all P values, <0.05).

Figure 3 shows the proportion of patients achieving glycemic control at 3 months and 6 months using an HbA_{1c} value less than 8% to define “in control.” At 3 months, about 34% of patients achieved glycemic control in both groups. At 6 months, 49% of patients in the glucose-only monitoring group compared with 34% of patients in the glucose-plus-fructosamine monitoring group were in control; this difference was not statistically significant ($P=0.10$).

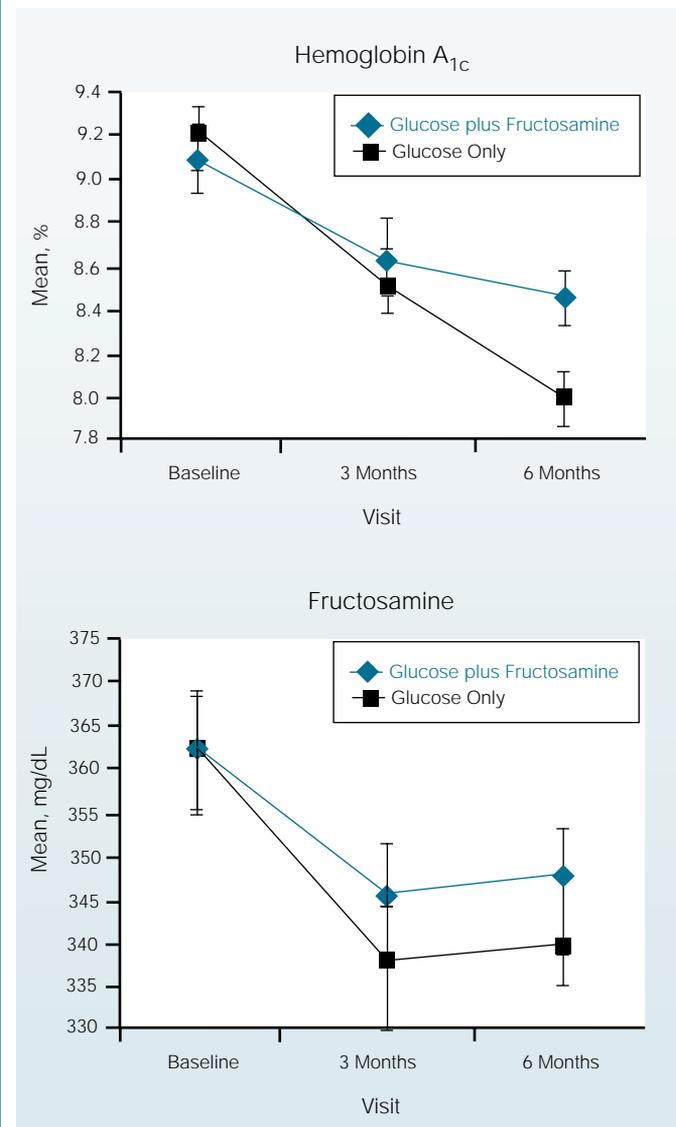


FIGURE 2. Mean levels of hemoglobin A_{1c} (top) and fructosamine (bottom) at baseline, 3 months, and 6 months.

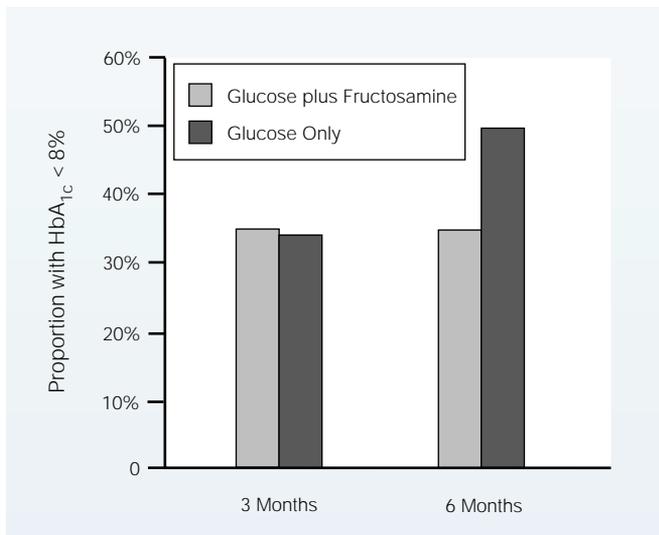


FIGURE 3. Proportion of patients with hemoglobin A_{1c} levels below 8% at 3 and 6 months.

Discussion

In this study, at-home measurement of fructosamine in addition to monitoring of glucose alone did not improve glycemic control in patients with type 2 diabetes and initially poor control. As a study of the effect of home monitoring of long-term glycemic control in improving control, the study had some limitations. First, by design, the intervention did not specify what changes in diet, drugs, or medical follow-up were to be initiated on the basis of the fructosamine test results. We also did not measure changes in diet or use of drugs, and we do not know the underlying reasons for the changes in glycemic control. Second, patients were not instructed to reduce the frequency of glucose monitoring based on the fructosamine results. Decreasing the need for glucose monitoring, and thus fingersticks, would be a major potential advantage of fructosamine monitoring.

Both groups had fairly large and statistically significant improvements in glycemic control compared with baseline. These improvements in glycemic control in the study participants could be due to regression to the mean, secular improvement in glycemic control, or “volunteer bias” (i.e., a selection process that produces a sample of patients ready to improve self-management).

In an attempt to assess these possibilities, we retrieved information on the HbA_{1c} values of the people with diabetes and an HbA_{1c} value greater than 8% who were mailed an invitation to participate but did not enroll; 114 of these people had one or more HbA_{1c} measurements in the 3- to 6-month interval after the invitation. This group of nonparticipants had a mean HbA_{1c} at the time of recruitment of 8.9% (compared with 9.2%

for trial patients) and experienced a 0.7% absolute decrease (compared with about 1% for trial patients overall). Unfortunately, the number of people who did not enroll in the study and had values for HbA_{1c} during the subsequent 6 months was small. These people, like the study volunteers, are a self-selected group who had more intense follow-up. Thus, the data do not rule out selection bias as an explanation for the improvements in glycemic control in the study participants and in this selected group. Regression to the mean also cannot be ruled out as an explanation for the results.

Per protocol, all of our study participants were contacted at least monthly by the study coordinator, and patients in the study received an average of seven calls. There was no difference in the number of study-related calls between the two groups. The study also educated both groups in the use of a glucose monitor and provided glucose strips and \$100 as payment for study completion. Another explanation for the improvements in glycemic control in the two intervention groups is that the study coordinator acted, inadvertently, as a case manager for both groups of patients and that the improvements are due to the case-management aspects of the study procedures.

Past research on case management of diabetes is of interest in this context. This literature is pertinent to all three explanations for the improvement in glycemic control we observed in both groups—regression to the mean, volunteer bias, and study-as-case manager.

A randomized study of nurse case management done in 17 type 1 and 121 type 2 diabetic patients in a group-model HMO found a decrease in HbA_{1c} of 1.7% in the case-managed group and 0.6% in the usual-care group.⁶ The difference in the decrease in HbA_{1c} between the case management group and the usual-care group was statistically significant. The results suggest an effect of the study procedures that was less than that of the case manager but still not negligible.

In contrast, a smaller randomized study of a pharmacist intervention involving 17 intervention and 22 control patients with type 2 diabetes showed that glycosylated hemoglobin levels decreased by 2.2% in intervention patients and 0.1% in control patients.⁷ The decrease in glycosylated hemoglobin was statistically significant only in the intervention patients, and there is no evidence of regression to the mean or of a study effect on glycemic control.

The possibility of study effects has implications for the design of behavioral intervention studies. There are many design trade-offs. To minimize study effects, study-related contact should be minimized. However, frequent contact might be needed to maintain participant interest and to assess compliance. To minimize

study effects, the intervention provided to the control or usual-care group should be limited. However, recruitment might be difficult if patients are informed that they will be assigned to no intervention. The possibility that payments to patients enhance study effects needs to be weighed against the effect of payment in enhancing compliance with study-related visits and reducing withdrawal.

The need for strategies to help patients self-manage diabetes to achieve good glycemic control persists. Although the addition of fructosamine monitoring to glucose monitoring did not improve glycemic control in this study, the approach remains promising for patients with type 2 diabetes. An assessment of the effects of replacing daily glucose monitoring with weekly fructosamine monitoring in patients who have achieved good control would be of particular interest. In this selected set of volunteers, self-monitoring of glucose combined with case-management approaches implemented as study procedures improved glycemic control. The possibility of regression to the mean or volunteer bias as explanations for the improvements cannot, however, be ruled out.

Take-Home Points

- Levels of fructosamine correlate with those of HbA_{1c} and can be measured by a monitor that patients use in the home.
- In a randomized trial of patients with inadequately controlled diabetes, we studied the effect of home fructosamine monitoring.
- There was no difference in glycemic control between the glucose-only and glucose-plus-fructosamine monitoring groups.
- Glycemic control in both groups improved substantially over the study period.
- Improvement may have been due to regression to the mean, volunteer bias, or the study protocol inadvertently having some case-managing effect.

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