Long-term Treatment of Type 1 Diabetes in the Outpatient Setting: Results of 934 Patients During up to 10 Years' Follow-up

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ABSTRACT

OBJECTIVE

To review the A1C levels of all patients with type 1 diabetes mellitus who returned for follow-up at the Diabetes Teaching and Training Centre, St. Paul's Hospital, Vancouver, British Columbia, Canada, and to correlate improvement in glycemic control with key aspects of diabetes management, including number of insulin injections per day, frequency of self-monitoring of blood glucose (SMBG) and hypoglycemic episodes.

METHOD

Up to 10-year follow-up data available for the 934 consecutive patients with type 1 diabetes who attended at least 1 follow-up session after completing a 4-day diabetes education program at the Diabetes Teaching and Training Centre from January 1984 to December 1999 were analyzed.

RESULTS

The average A1C was 9.2±2.0% standard deviation (SD) at baseline. A1C decreased significantly from baseline at follow-up visits to 8.4±1.0% at 1 year, 8.4±1.9% at 5 years, and 8.2±2.2% at 10 years ($p<0.0001$ vs. baseline).

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RÉSUMÉ

OBJECTIF

Mesurer les taux d'HbA_{1c} de tous les patients atteints de diabète de type 1 qui se sont présentés pour des examens de contrôle au Diabetes Teaching and Training Centre, St. Paul's Hospital, Vancouver (Colombie-Britannique) Canada, et mettre en corrélation l'amélioration de l'équilibre glycémique et les principaux aspects du traitement du diabète, y compris le nombre d'injections d'insuline quotidiennes et la fréquence de l'auto-surveillance de la glycémie et des épisodes d'hypoglycémie.

MÉTHODE

On a analysé les données recueillies pendant jusqu'à 10 ans auprès de 934 patients consécutifs atteints de diabète de type 1 qui se sont présentés au moins une fois pour un examen de contrôle après avoir suivi un programme de formation de 4 jours sur le diabète au Diabetes Teaching and Training Centre entre janvier 1984 et décembre 1999.

RÉSULTATS

L'HbA_{1c} moyenne était de 9,2 ± 2,0 % écarts types au départ. L'HbA_{1c} avait baissé significativement par rapport au départ aux consultations de suivi, soit de 8,4 ± 1,0 % après 1 an, de 8,4 ± 1,9 % après 5 ans et de 8,2 ± 2,2 % après 10 ans ($p < 0,0001$ par rapport au départ).

CONCLUSION

On peut obtenir des améliorations significatives et prolongées de l'HbA_{1c} chez les patients atteints de diabète de type 1 qui se présentent pour des examens de contrôle après avoir suivi un programme exhaustif d'éducation diabétologique à l'intention de patients non hospitalisés. Au fil du temps, on a observé une hausse de la fréquence de l'auto-surveillance de la glycémie ($p < 0,0001$), une hausse du nombre d'injections d'insuline quotidiennes ($p < 0,0001$) et une tendance à la baisse du nombre d'épisodes d'hypoglycémie signalés par le patient ($p < 0,055$). L'amélioration de

CONCLUSION

Significant and long-term improvements in A1C can be achieved in patients with type 1 diabetes who return for follow-up after attending a comprehensive outpatient diabetes education program. An increased frequency of SMBG ($p<0.0001$); an increase in the number of insulin injections per day ($p<0.0001$) and a trend toward decreased self-reported hypoglycemia ($p<0.055$) were observed over time. Improvement in glycemic control was related to increased frequency of SMBG and occurred without an increase in the number of hypoglycemic episodes.

la maîtrise de la glycémie était liée à une hausse de la fréquence de l'auto-surveillance et s'est produite sans qu'il y ait de hausse du nombre d'épisodes d'hypoglycémie.

INTRODUCTION

The Diabetes Control and Complications Trial (DCCT) documented improvement in long-term glycemic control in patients with type 1 diabetes mellitus who were specifically recruited for the study and were randomly assigned to intensive insulin therapy (1). However, this group of patients also required frequent follow-up and intense supervision by healthcare professionals (1). Participation in a diabetes education program has been shown to improve glycemic control, but only in the short term (2-4). Substantial evidence is now available to support the relationship between estimates of glycemic control and the development of long-term complications of diabetes (1,5-9). The goals of therapy in patients with type 1 diabetes now focus on the prevention or delay of diabetes complications in all patients. The interventions used to achieve these goals must be practical, effective and cost-effective. There are few large-scale, long-term evaluations of the treatment of type 1 diabetes in unselected patient populations, and such studies tend to show little or no effect of interventions on estimates of diabetes control (3). This paper reports the glycemic control achieved by a large cohort of patients with type 1 diabetes who returned for up to 10 years' follow-up at a diabetes centre after attending a 4-day diabetes education program as outpatients.

METHOD

The 4-day diabetes education program at the Diabetes Teaching and Training Centre, St. Paul's Hospital, Vancouver, British Columbia, Canada, consists of 4 consecutive days of attendance at the multidisciplinary centre. During the program, patients eat all meals at the centre with direct supervision by nutrition staff. Information about general aspects of diabetes, nutrition therapy, meal planning, management of sick days, restaurant dining, alcohol use and foot care is provided in group education sessions. Patients also receive individual instruction on nutrition, insulin injection and self-monitoring of blood glucose (SMBG). Each patient has daily meetings with an endocrinologist who may make changes to the patient's treatment.

After completion of the 4-day program, the patient is scheduled to attend a 1-day follow-up program at the centre, usually in 6 months' time. The 1-day follow-up program is a review of the information patients received during the 4-day program and/or provides supplemental information to patients who have already received adequate diabetes education. Subsequent follow-up visits to the centre are usually scheduled annually thereafter. Interim diabetes management is provided by the attending endocrinologist or family physician.

Data from 934 consecutive patients with type 1 diabetes who returned for at least 1 follow-up visit after completion of the 4-day diabetes education program from January 1984 to December 1999 were extracted from a computer-based database and were analyzed. An additional 513 patients were not included in the analysis because they did not return for a follow-up visit after completion of the 4-day program. One possible reason why some patients did not return for a follow-up visit was because 9% of the patients lived >160 km from the centre. During the study period, 34 deaths occurred. The patients' baseline data at the start of the 4-day program were used as a historical control. Eighty-eight percent of the patients had been diagnosed with diabetes at least 1 year prior to their first visit to the centre. Patients were categorized as having type 1 diabetes if they were using insulin therapy and met at least 1 of the following criteria: 1) age at onset of diabetes <30 years; 2) history of proven diabetic ketoacidosis (in a patient requiring insulin therapy); or 3) negative C-peptide challenge. A1C was recorded at each visit. The frequency of SMBG and number of daily insulin injections were also documented. Frequency of hypoglycemia was self-reported as the number of times per month the patient felt that they had experienced a hypoglycemic episode or was observed by others to have hypoglycemia.

During the study, 2 different techniques were used to measure A1C. From January 1984 to April 1990, a cation-exchange resin in a disposable column (HbA_{1c} Microcolumn test, Bio-Rad Laboratories, Hercules, California, United States [US]) was used to measure A1C. From May 1990 to December 1999, the centre used an ion-exchange high-performance liquid chromatography (HPLC) technique (Diamet analyzer, Bio-Rad Laboratories, Hercules, California, US). Blood specimens were collected in Vacutainer® tubes containing ethylenediamine tetraacetic acid (EDTA) as the

anticoagulant (BD Biosciences, Franklin Lakes, New Jersey, US). The 2 methods were compared using 226 samples from patients attending the diabetes centre. For the purpose of this report, the Microcolumn test results were adjusted according to the derived linear regression model, i.e. Diamet result = 0.001 + 1.127 x (Microcolumn result), r=0.95.

The Generalized Estimating Equation (GEE) model (10) was used to evaluate A1C levels over time, with A1C as the response variable and time from baseline (years) as the predicator variable; frequency of SMBG; number of insulin injections and frequency of hypoglycemia over time. Spearman's rank correlation coefficient was used to assess the relationship between A1C, frequency of SMBG and hypoglycemic episodes. The Kruskal-Wallis test was used to compare the mean frequency of SMBG and hypoglycemic episodes between A1C quartiles (<7.7%, 7.7% to 8.6%, 8.7% to 9.6%, >9.6%) at baseline, 5 years and 10 years.

RESULTS

During the observation period (January 1984 to December 1999), 1447 patients attended the 4-day diabetes education program, of which 934 (64.5%) returned to the centre for at least 1 follow-up visit and 513 (35.5%) were lost to follow-up (never returned to the centre). The 934 patients (55.5% male) included in the study had a mean±standard deviation (SD) age of 44.0±13.2 years and a duration of diabetes of 21.2±12.2 years (Table 1). Program participants included those with new-onset type 1 diabetes and those with a longer duration of diabetes; however, only 12% of patients had been diagnosed with type 1 diabetes during the same year as their first visit to the centre.

Table 1. Patient profile

Characteristics	*Patients (n=934)*
Age at baseline (years±SD)	44.0±13.2
Duration of diabetes (years±SD)	21.1±12.2
Male sex (%)	55.5

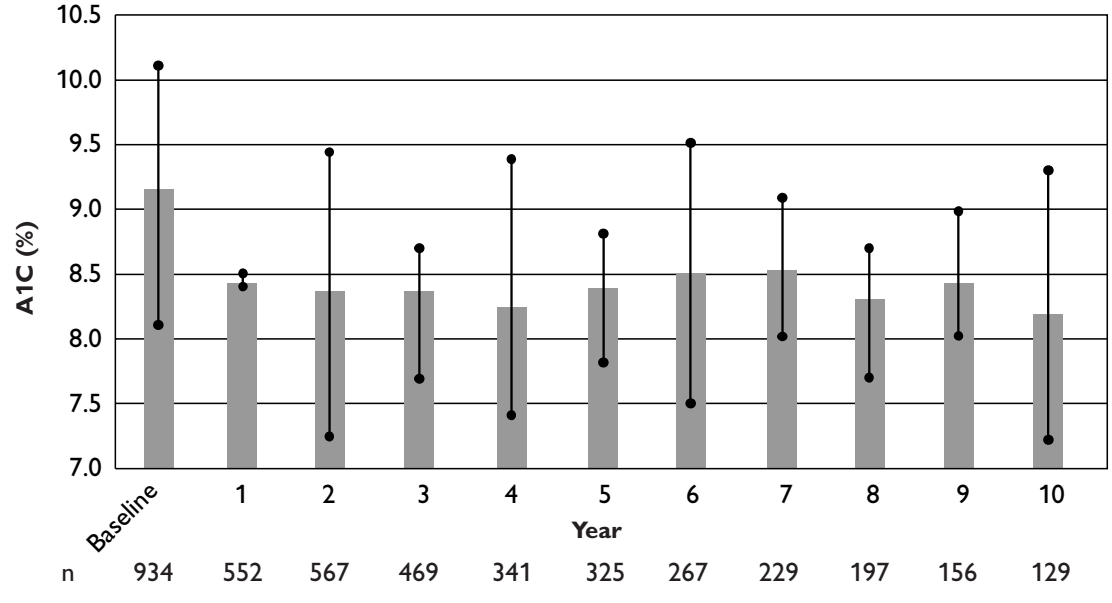
Analysis of the available follow-up data for 934 patients revealed that not all patients returned to the centre at the recommended intervals, and return rates declined after the first year. The average number of follow-up visits during the observation period was 4.7 visits. At follow-up, A1C levels had decreased from baseline and remained improved in those patients who returned to the clinic during the 10-year observation period (Figure 1). Significant reductions in A1C were observed each year compared to baseline ($p<0.0001$ for years 1 to 10).

The percentage of patients with A1C levels in each A1C quartile (<7.7%, 7.7% to 8.6%, 8.7% to 9.6%, >9.6%) each year (baseline to year 10) is shown in Figure 2. A1C was >9.6% in 35% of patients at baseline and in an average of 20% of patients during follow-up. A1C was <7.7% in 20% of patients at baseline and in an average of 30% of patients during follow-up.

The number of insulin injections per day increased during the 10-year observation period. The frequency of insulin injections was not significantly different between A1C quartiles.

Patients reported hypoglycemic episodes to their endocrinologist. The mean number of hypoglycemic episodes experienced per month by patients in each A1C quartile at baseline, 5 years and 10 years is shown in Figure 3. At baseline, A1C was negatively correlated with mean number of hypoglycemic episodes per month ($p<0.0001$). At 5 years and 10 years,

Figure 1. Average A1C levels of 934 patients at baseline and each year for up to 10 years



there was a trend toward a reduction in the number of hypoglycemic episodes, but it did not reach statistical significance ($p<0.055$). The frequency of hypoglycemia at baseline was significantly different between A1C quartiles ($p<0.0001$): patients with lower A1C levels experienced a higher frequency of hypoglycemic episodes than those with higher A1C levels. However, no difference in the frequency of hypoglycemic episodes was observed between quartiles at 5 years and 10 years.

Figure 4 shows the mean number of times SMBG was performed per week by patients in each A1C quartile at baseline, 5 years and 10 years. A1C values were negatively correlated with the frequency of SMBG at baseline ($p<0.001$) and 5 years ($p<0.008$). At year 10, this correlation was not statistically significant. A correlation between all quartiles and frequency of SMBG was observed at baseline ($p<0.0001$), but was not maintained at 5 years ($p=0.057$). However, the frequency of SMBG by the entire study population increased over time ($p<0.0001$).

DISCUSSION

During the observation period, 934 patients returned to the centre for at least 1 follow-up visit and were included in the study. Long-term improvement in glycemic control, estimated based on A1C, was observed in those patients who returned for follow-up. The average A1C levels in this study were similar to those reported in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up

Figure 2. Percentage of patients with A1C levels within each A1C quartile each year from baseline to year 10

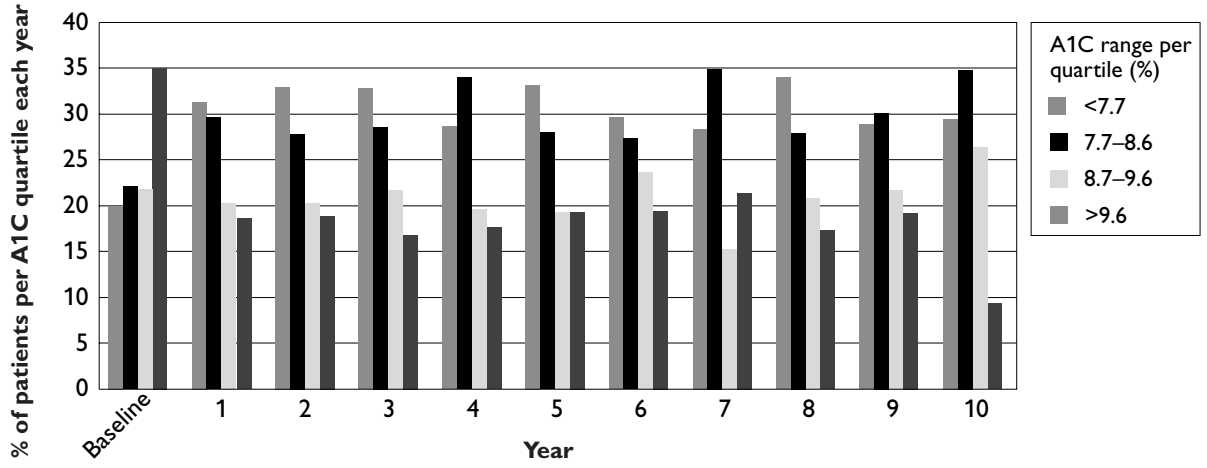


Figure 3. Mean number of hypoglycemic episodes experienced per month at baseline, 5 years and 10 years for each of the A1C quartiles

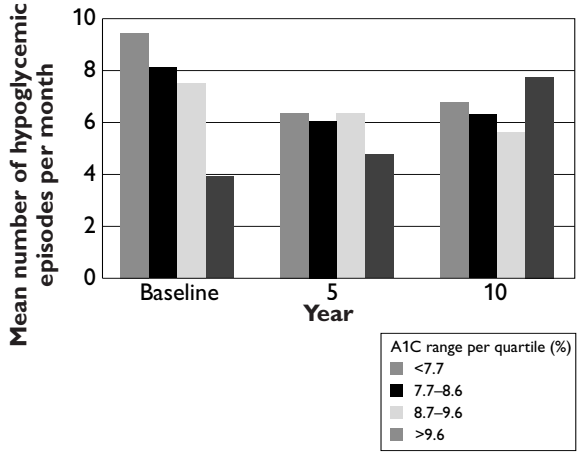
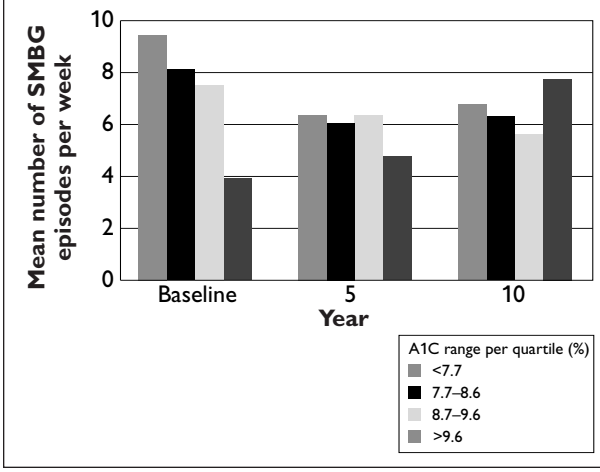


Figure 4. Mean number of times SMBG performed per week at baseline, 5 years and 10 years for each of the A1C quartiles



SMBG = self-monitoring of blood glucose

study of the DCCT cohort (11). During the first 2 years of the EDIC, the cumulative mean±SD A1C levels were 8.2±1.3% in men and 8.3±1.5% in women, results similar to those of the current study (mean A1C: 8.4±1.0% in year 1 and 8.4±1.6% in year 2 [men and women combined]) (11).

A substantial number of patients were lost to follow-up in the current study; no data are available for those patients who did not return to the centre, except that compared to those who returned, they did not differ in age, baseline A1C, weight or duration of diabetes.

The majority of patients included in the study were using 2 insulin injections per day and no extraordinary treatment interventions were made. Although the degree of improvement in glycemic control is not equal to that observed in the DCCT, glycemic control significantly improved compared to baseline, and approximates the preliminary results of the EDIC (11). In contrast to the rigorous process used to select patients for inclusion in the DCCT and EDIC, the patients involved in the current study were selected solely on the basis of their willingness to attend and return to the centre.

A correlation between the frequency of self-reported hypoglycemic episodes and A1C levels was initially observed, but was not maintained beyond baseline. This differs from the results of the DCCT but is in agreement with findings in children (12,13). One explanation may be that, on average, the reductions in A1C were not large enough to increase the frequency of hypoglycemia. An average reduction in hypoglycemic episodes was observed over time.

No correlation was found between the frequency of insulin injections and A1C levels. However, the frequency of insulin injections increased in the study population over time. The majority of patients included in the study used 2 injections of insulin per day, with a treatment goal of A1C <8.0% (normal range: 4.0% to 6.0%).

In the entire study population, the frequency of SMBG and A1C were correlated at baseline and at 5 years. This correlation was observed in A1C quartiles at baseline but not at 5 years or 10 years. The frequency of SMBG significantly increased in the entire study population over time ($p<0.0001$).

Since improved glycemic control is associated with a reduction in the frequency and severity of complications, this method of diabetes therapy appears practical and effective for those who return to the diabetes centre for follow-up.

Of all patients with type 1 diabetes who attended the 4-day diabetes education program, 64.5% returned for at least 1 follow-up visit. However, there was a tendency for patients to return to the centre after long periods of absence. In a previous study that analyzed 556 patients with 2346 visits to the centre, delay in follow-up (>2 years) resulted in significant deterioration of glycemic control, as estimated by A1C (14). This may have been a reason why greater improvements in follow-up A1C levels were not observed in the present study. In those patients who returned to the centre, maintenance of the initial improvement in A1C was observed for up to 10 years. The patients in this study represent a selected population in that they attended a diabetes education program and returned for follow-up. In this group of patients, long-term, significant improvement of diabetes control is achievable. This improvement is related to an increased frequency of SMBG and can occur without significant increase in hypoglycemia.

The average reduction in A1C of 1.0% was maintained during the 10-year observation period and likely has implications on healthcare costs. Data from the DCCT have been used to estimate the benefits of reductions in A1C on healthcare costs and have demonstrated the beneficial effects of the increased use of intensive insulin therapy (15). Others have shown a correlation between A1C levels and healthcare costs (16). Costs were related to age and to the presence of comorbid conditions such as heart disease and hypertension. Changes in A1C of 1.0% were associated with a 7.0% difference in costs. Extrapolation of the conclusions of Gilmer and colleagues to the current study population suggests an estimated reduction in healthcare costs per patient of US $290 to $1030 per year (16). Extrapolation based on the data from the DCCT suggests an estimated decrease in the progression of retinopathy of approximately 33%.

The long-term improvement in glycemic control experienced by a large number of patients with type 1 diabetes involved in a general hospital-based diabetes education and treatment program provides a model that others can use to improve and maintain glycemic control in patients with type 1 diabetes.

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