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Longitudinal Patterns of Glycemic Control and Diabetes Care from Diagnosis in a Population-based Cohort with Type 1 Diabetes

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Glycosylated hemoglobin is an indicator of long-term glycemic control and a strong predictor of diabetic complications. This paper provides a comprehensive description of glycemic control (total glycosylated hemoglobin (GHb)) up to 4.5 years duration of diabetes by age, duration, and sex in a population-based cohort (n = 507) aged less than 20 years followed from diagnosis of Type 1 diabetes in Wisconsin during 1987–1994. Important aspects of demographics and diabetes care are described to allow comparison with other populations. Since large variations between laboratories are known to exist in the measurement of GHb, levels are also interpreted relative to the frequency of short-term complications. GHb increased after diagnosis, but leveled off after 2–3 years. Peak GHb values occurred in the age group 12–15 years. The within-individual standard deviation in GHb between tests, adjusted for age and duration, was 1.6%. The mean GHb at last testing was 11.3%, with a standard deviation across individuals of 2.9%. The majority (74%) of individuals saw a diabetes specialist at least once. The mean number of insulin injections per day increased from 2.2 to 2.5 across the 4.5-year duration, and the insulin dose increased from 0.6 to 0.9 units per day per kg body weight. Despite the quite satisfactory level of care, 38% of subjects had GHb levels associated with significant short-term complications. *Am J Epidemiol* 1996;144:954–61.

blood glucose; diabetes mellitus, insulin-dependent; hemoglobin A, glycosylated; longitudinal studies

Over the past decade, measurement of glycosylated hemoglobins has become the established method for monitoring glycemic control in Type 1 diabetes. Results of recent clinical trials such as the Diabetes Control and Complications Trial (DCCT) and other randomized studies have demonstrated that effort aimed at improved glycemic control is key for preventing chronic microvascular complications (1–3). Data from the DCCT suggest ranges of glycemic control that are desirable and achievable in highly committed patient groups working with large support staffs under ideal conditions (1). These results need to be supplemented by those from population-based observational studies to indicate what levels of intensity of care and glycemic control are found in the general population of individuals with Type 1 diabetes.

A few previous studies have addressed glycemic control in large samples (4–9). The earliest report investigated glycosylated hemoglobins cross-sectionally from 1979 and 1980 in the Diabetes Clinic at the Children's Hospital in Pittsburgh, Pennsylvania (4). Its results may not represent today's diabetes management situation because 90 percent of patients used a single daily insulin injection. Another study described glycosylated hemoglobin A_1 (HbA_1) levels in a cross-sectional sample in southern Wisconsin, during 1980–1982 (5), with follow-up in 1984–1986 (6). Still, 55 and 36 percent of the population, respectively, were using one daily insulin injection. A more recent cross-sectional study described levels of glycosylated hemoglobin A_{1c} (HbA_{1c}) in nationwide screening in Denmark from December 1986 to April 1987 and in 1989 (7, 8). With an average of three insulin injections per day, the intensity of care was higher than in US population-based cohorts. Even recently, only 13.5 percent of patients with Type 1 diabetes in the United States were found to use three or more daily injections (10).

Our data are unique in providing information on glycemic control in a population-based incident cohort

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Abbreviations: DCCT, Diabetes Control and Complications Trial; GHb, total glycosylated hemoglobin; HbA_1, glycosylated hemoglobin A_1; HbA_{1c}, glycosylated hemoglobin A_{1c}.

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from diagnosis. It has been proposed that glycemic levels in the early course of diabetes have special importance (3, 11–13). A previous report on our cohort (9) included data only up to 2 years postdiagnosis. Since we now have total glycosylated hemoglobin (GHb) determinations on 3,675 samples from 507 individuals aged 0–19 years for up to 4.5 years duration, we are in a position to comprehensively describe early variation and trend in GHb by the major factors of age, sex, and diabetes duration.

MATERIALS AND METHODS

Population

All individuals with newly diagnosed Type 1 diabetes from 28 counties in south central Wisconsin were invited between May 1987 and April 1992 to enroll in the study. Diabetes was defined by classic symptoms of polyuria and polydipsia with initiation of exogenous insulin use. This analysis includes all GHb data collected within ages 0–19 years and within the 0–4.5 years duration window, which comprises 507 individuals.

Recruitment proceeded by physician, nurse, and educator referral and by self-report. All hospitals and most multipractice clinics in the study area were telephoned every 3 months to ascertain any cases missed by referral. Among those hospitalized at diagnosis, completeness of ascertainment is estimated at 97 percent for children and 82 percent for adolescents. The participation rate was 82 percent among those identified. Those eligible for recruitment represent an incidence of 14.0 per 100,000 in the underlying population aged 0–19 years during the study period.

Data collection

Demographic information, including birth date, parental education level, parental occupation, ethnicity, and sex, was collected by telephone interview 2–3 months after diagnosis. Socioeconomic level was assigned by the scheme of Stevens and Cho (14), which is based on 1980 US census occupational categories. The diagnosis date was determined from hospital or clinic records.

Starting 3–4 months after diagnosis, subjects were asked to submit a blood specimen at each routine visit to their local physician or clinic, or every 4 months if no visit was scheduled. Kits containing 5-ml ethylenediaminetetraacetic acid-treated tubes and postage were provided. Aspects of diabetes management (number of injections, insulin dose, and contact with specialists) were ascertained by questionnaires mailed every 6 months. The questionnaire also inquired about diabetes-related hospitalizations since last contact. All hospitalizations were verified by record abstracting.

Dietary compliance was collected at an examination 4 years after diagnosis, using data categories of following a prescribed diabetic diet never, at least 25 percent, 50 percent, or 75 percent of the time. Subjects from the 15 counties nearest to the central laboratory were asked for a 24-hour urine specimen at 3–4 months and at 4 years after diagnosis for determination of C-peptide, a measure of endogenous insulin production.

Specimen handling and testing

Whole blood was delivered in styrofoam to the study's central laboratory, where it was immediately processed. Blood samples were analyzed for GHb within 7 days by Isolab Glycaffin (Isolab, Akron, Ohio) microcolumn affinity chromatography. Assays were repeated when any duplicate within-assay values differed by more than 2.5 percent of their mean. Internal standards stored at −70°C were evaluated routinely for stability over time and showed no trend. Within-assay variability was ±1.1 percent for case samples and ±0.9 percent for internal standards. These standards from nondiabetic pediatric and young adult subjects had mean GHb (±standard deviation) of 5.5 ± 0.77 percent.

Urine was collected in a clean amber container and initially frozen at −20°C for 12–36 hours. At the central laboratory, it was thawed, adjusted to a pH of 7–8, and frozen at −80°C until testing. C-peptide was measured in triplicate by radioimmunoassay with guinea pig antisera M1221 and ^{125}I-labeled C-peptide using the standard kit from Novo (Bagsvaerd, Denmark (15)). The working range of the standard curve was 0.05–3.00 pmol/ml. The between-assay coefficients of variation ranged from 16 percent for urine with less than 1 pmol/ml to 8 percent at 18–23 pmol/ml. Data reduction and analysis were performed by the four-parameter logistic curve-fitting program of Rodbard (16). A level above 0.03 pmol/ml was considered detectable C-peptide.

Statistical methods

For comparison with previous cross-sectional studies and the DCCT, GHb and number of insulin injections per day at last measurement were used for descriptive analysis. Other analyses used all available longitudinal data outlined above.

Since the effects of age at diagnosis, duration of Type 1 diabetes, and age at time of GHb testing (hereafter referred to as age at test) cannot be simultaneously estimated, initial analyses were aimed at

choosing two of the three for further analyses. Duration is of intrinsic importance in Type 1 diabetes. Plots of GHb versus duration and age at diagnosis showed that the peak GHb for each age cohort occurred at age at test of approximately 15 years. This implied that using age at test would likely yield results of greater simplicity and interest. Graphs and regression analyses therefore use duration (in years) and age at test (in years) as the independent variables. In graphs, mean GHb is presented by 4-year age at test intervals and 0.5-year duration intervals. This grouping yielded sample sizes of at least 25 in all subgroups.

The effects of age at test and duration were examined by mixed effects regression analysis using the program of Cook as modified by Stram (17). The significance of all quadratic and cubic terms as well as all interaction effects between the two variables was determined. Once a satisfactory model was achieved, sex was introduced as a main effect and in all two-way interactions. The final model was checked by comparison of observed and expected mean GHb.

In the mixed-effects model, the between- and within-individual variability in GHb were explicitly modeled. Likelihood ratio tests were used to test the significance of variance components while adjusting for trends in GHb by duration and age. The residual variability after separating out all significant sources of between-individual variability was used as the estimate of variability between test occasions. Confidence intervals for mean GHb from the model were also obtained from the mixed-effects modeling.

Since we do not intend to draw inferences regarding efficacy or effectiveness of diabetes management approaches, the number of insulin injections per day, insulin dose per kg and day, compliance with diet, contact with specialist, and urine C-peptide were analyzed by descriptive procedures. Means and percentages are presented by age groups (and duration, when applicable). Hospitalization rate was computed as the number of diabetes-related hospitalizations divided by the total person-years of follow-up for groups defined by mean GHb. The significance of the relation between the rate and GHb level was tested in Poisson regression by the procedure of Liang and Zeger (18) by using an independence working correlation and a robust estimate for the standard error of the regression coefficient.

Data completeness

Children below age 4 years supplied only basic body measurements at the clinical examinations. Among those age 4 and above, there were 442 subjects in the baseline examination data set. For geographic reasons, 98 were not invited to submit initial urine, leaving 344 eligible for the C-peptide test. Of these, 83 percent (n = 286) submitted urine, resulting in 83, 83, 82, and 86 percent having the determination in the four age groups, 4–7, 8–11, 12–15, and 16–19 years, respectively. A total of 341 individuals in the analyzed group reached a duration of 4 years while remaining in the 4- to 19-year age window. Of these, 73 percent (n = 249) provided urine at 4 years, or 81, 79, 72, and 60 percent by age group. Dietary compliance data at 4-year follow-up were provided by 87 percent (n = 297), or 89, 93, 85, and 80 percent by age group.

The number of blood samples for GHb determination ranged from 1 to 16 per person, with 21 percent submitting three or fewer samples and 9 percent submitting over 12. The remainder were approximately evenly spread between 4 and 11 samples each. As a measure of completeness, the number of samples submitted per year of follow-up (termed the "compliance index") was computed for each person. The overall mean for this variable was 2.1 samples per year, with means of 2.3, 2.3, 2.1, and 2.0 for the four age groups. Adding the compliance index to the final model allowed examination of trends with age and duration adjusted to the representative mean compliance of the entire cohort.

The return rate for biannual questionnaires on diabetes management and hospitalization was 80 percent overall (among 501 individuals with at least one questionnaire), with age group rates of 83, 81, 78, and 80 percent, respectively.

RESULTS

Descriptive cross-sectional information

Descriptive demographic information on our sample is provided in table 1. The socioeconomic level of 40.58 in the cohort corresponds to a mean of 36.35 with a standard deviation of 18.94 in the US labor force (14). A level of 41 describes "legal assistants," while 36 corresponds to "construction inspectors."

The distribution of GHb using the last measurement for each individual is shown in figure 1. The modal GHb was 10–11 percent at mean duration of 3.0 years and mean age of 12.4 years. The cross-sectional median GHb was 10.9 percent, the mean was 11.3 percent, and the standard deviation was 2.9 percent. Descriptive statistics for the subgroup aged 13–17 years (n = 167) corresponding to a report from the DCCT (19) were: median, 11.8; mean, 12.0; and standard deviation, 3.5 percent. The cross-sectional number of insulin injections per day had a mean of 2.5 and ranged from 1 to 4, but 95 percent of all individuals used two or three injections.

TABLE 1. Characteristics of the study population (diabetic persons less than age 20 years, Wisconsin, 1987–1994 (n = 507)

Characteristic	Description
Age (years) at diagnosis of type 1 diabetes (mean (SD*))	9.4 (4.6)
Duration (years) of type 1 diabetes at last measurement (mean (SD))	3.0 (1.2)
No. of males (%)	259 (51)
No. of Caucasians (%)	474 (94)
Socioeconomic level of parents (mean (SD))	40.58 (19.91)
Mother's education (years)	13.6 (2.2)
No. of samples per individual (mean (range))	7.3 (1–16)
% glycosylated hemoglobin at last test (mean (SD))	11.3 (2.9)
No. of insulin injections per day at last questionnaire (mean (range))	2.5 (1–4)

* SD, standard deviation.

Descriptive longitudinal information on glycemic control

With our entire data set, mean GHb by diabetes duration and age subgroups is shown in figure 2. GHb increased with duration up to approximately 2–3 years and leveled off thereafter. GHb is seen to peak at 12 percent in adolescents aged 12–15 years, with markedly lower levels (by about 2 percent) both above and below this age interval. Children under age 12 years leveled sooner (at 1.5–2 years), and persons above 16 years tended to drop in GHb after reaching their peak at 3 years duration.

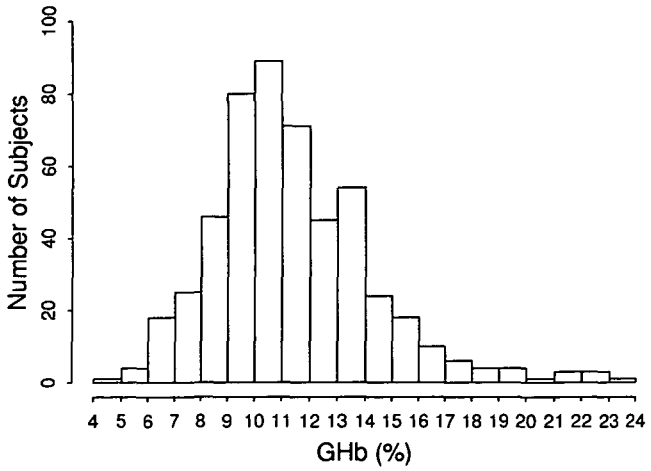

FIGURE 1. Distribution of total glycosylated hemoglobin (GHb) at last test occasion (mean duration, 3.0 years; mean age, 12.4 years) (n = 507) for diabetic persons less than age 20 years in Wisconsin, 1987–1994.

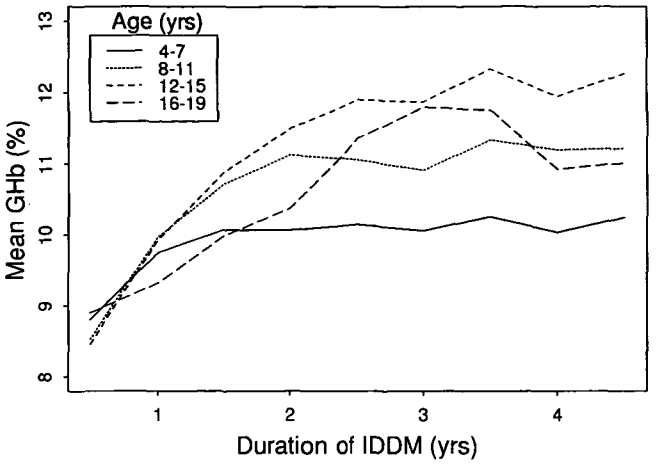

FIGURE 2. Mean total glycosylated hemoglobin (GHb) by duration in four age groups as obtained by raw data (n = 74, 123, 151, 121, and 38 by age group at diagnosis) for diabetic persons less than age 20 years in Wisconsin, 1987–1994.

Regression analysis of trends with age, duration, and sex

Regression analysis showed age and duration to be independently associated with GHb. However, as seen in the raw data (figure 2), these trends were not linear, and duration trends differed between age groups. Thus, quadratic and cubic terms for age and duration were added, as well as interaction effects between the two. The coefficients for the final equation are given in table 2, and the model is illustrated in figure 3.

GHb as predicted by the model is presented in figure 3. Comparison of figures 2 and 3 verifies a good fit, except possibly for the age group 16–19 years. This group contained fewer individuals than the other three. Interaction terms for sex with age and duration were not statistically significant. A slightly higher level (of 0.20 percent) of GHb in males was also not significant. The compliance index was significantly associated with GHb (adjusted coefficient of −0.6 percent/yearly

TABLE 2. Estimates of linear regression coefficients for prediction of glycosylated hemoglobin (n = 507) for diabetic persons less than age 20 years, Wisconsin, 1987–1994

Variable	Estimated coefficient	p value
Intercept	11.584	0.0001
Age (years)	−0.991	0.0001
Age^2	0.086	0.0013
Age^3	−0.003	0.0077
Duration (months)	0.965	0.0259
Duration^2	−0.913	0.0001
Duration^3	0.126	0.0001
Age × duration interaction	0.323	0.0001
Age^2 × duration interaction	−0.007	0.0318
Age × duration^2 interaction	−0.023	0.0040

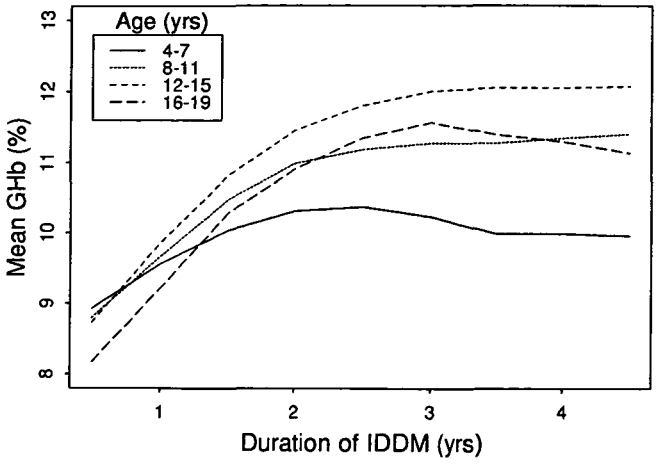

FIGURE 3. Mean of individual regression predictions for total glycosylated hemoglobin (GHb) by duration in four age groups as obtained by model in table 2 (n = 74, 123, 151, 121, and 38 by age group at diagnosis) for diabetic persons less than age 20 years in Wisconsin, 1987–1994.

sample returned, $p = 0.001$), and the graph was redrawn with adjustment for this variable (not shown). The same duration trends remained, with a slight widening of age differences and approximately 0.3 percent higher GHb overall.

The 95 percent confidence intervals for the model were narrower than ±1.0 percent for all durations and ages and narrower than ±0.4 percent for ages less than 16 and duration up to 4 years.

Estimation of variability in GHb

Individuals varied significantly in GHb level even after adjustment for age and duration ($p < 0.001$) and also in their trends with age and duration ($p < 0.001$). Our model represents the average across these varying individual trends.

Taking into account the interpersonal variability and adjusting for age and duration trends resulted in an estimated test-to-test standard deviation in GHb for a given individual of 1.6 percent. After age and duration were taken into account, the cross-sectional standard deviation was 2.8 percent, implying that approximately $1 - (1.6^2/2.8^2) = 0.67$ of variability can be attributed to unspecified individual factors.

Aspects of diabetes care

Overall, 74 percent were seen by a diabetes specialist at least once. The percentage was highest in the lowest age group (84 percent in children aged 4–7 years) and decreased by age (76, 72, and 63 percent, respectively, for those aged 8–11, 12–15, and 16–19 years). Four-year follow-up data indicated that by age group 91, 90, 78, and 63 percent ate a prescribed diabetic diet at least 50 percent of the time. Conversely 9, 7, 15, and 29 percent followed such a diet none of the time. Figures 4 and 5 show an increasing need for insulin with duration in all age groups. The youngest age group experienced the most intensive care in terms of number of injections per day. Insulin dose per kilogram, however, was the highest for the adolescent group. These findings may be seen in the context of 89, 90, 93, and 91 percent, respectively, having detectable C-peptide at baseline for the four age groups, respectively, and 4, 6, 25, and 50 percent having detectable C-peptide at 4-year follow-up.

Interpretation of GHb levels relative to short-term complication

To provide a context for assessing the level of glycemic control, table 3 shows information on hospitalization rate. There is a significant relation ($p < 0.001$) between hospitalization and GHb, with sharp increases in hospitalization rate at GHb levels of 11 and 13 percent. Approximately 38 percent of all subjects had mean GHb level of at least 11 percent, and 13 percent had mean GHb level of at least 13 percent.

DISCUSSION

Our study provides a comprehensive description of glycemic control as reflected by GHb in the first 4 and a half years after diagnosis in a population-based cohort receiving the range of current care in our region. The data we present should be useful for comparison with other past and present populations of children, adolescents, and young adults with Type 1 diabetes. The cohort resulted from an incidence during the accrual period of 14.0 per 100,000 population aged 0–19

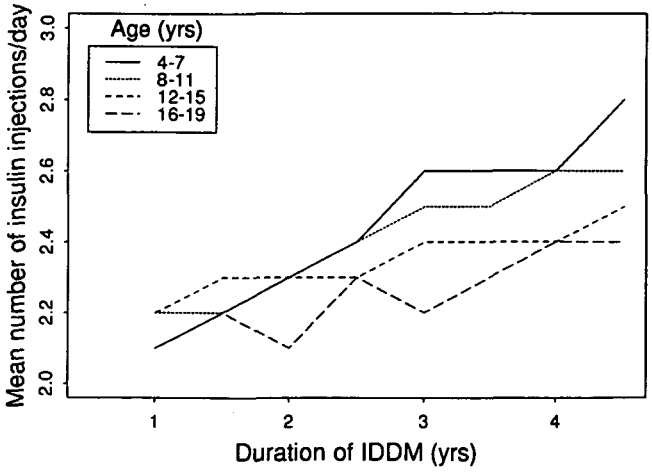

FIGURE 4. Mean number of insulin injections per day by age group and duration of Type 1 diabetes (n = 72, 123, 150, 119, and 37 by age group at diagnosis) for diabetic persons less than age 20 years in Wisconsin, 1987–1994.

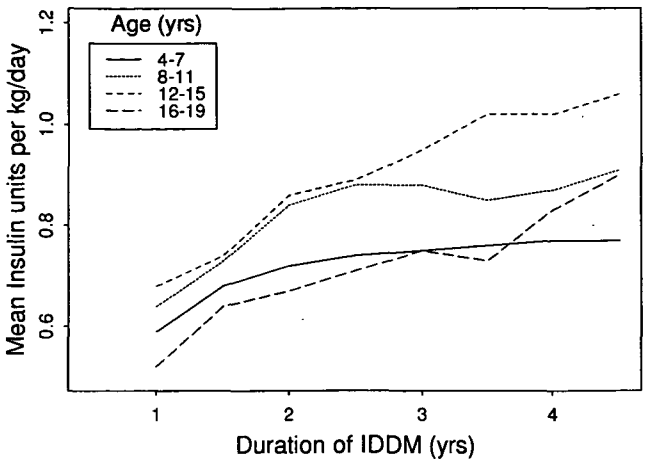

FIGURE 5. Mean insulin units per kg per day by age group and duration of Type 1 diabetes (n = 72, 123, 150, 119, and 37 by age group at diagnosis), for diabetic persons less than 20 years of age in Wisconsin, 1987–1994.

TABLE 3. Hospitalization rate by glycosylated hemoglobin level for diabetic persons less than age 20 years, Wisconsin, 1987–1994

Glycosylated hemoglobin range (%)	No.*	Rate of hospitalization†
<7	18	0.05
7–<9	100	0.05
9–<11	191	0.07
11–<13	127	0.11
≥13	65	0.20

* Number responding to hospitalization question on questionnaire.

† Rate of diabetes-related hospitalizations per person-year of follow-up.

years. Adjusted to the standard population used in a previous study of a Wisconsin region (20), our rate corresponds to 14.2 per 100,000 compared with 16.7 in that study. Standardized to the same population, previous reports from Denmark (21) and Pennsylvania (22) showed incidences of 13.9 and 14.8, respectively, in the age group 0–19 years. Thus, our incidence corresponds well with that in other studies.

Using the GHb measurement at the last test occasion, our mean GHb of 11.3 percent is 0.5 percent lower than in Pittsburgh in 1979–1980 at comparable age and duration (4). A group aged less than 18 years containing 164 individuals in the 1980–1982 Wisconsin Diabetic Retinopathy Study had mean HbA_1 of 11.0 percent, and a follow-up in 1984–1986 on the same cohort suggested that GHb had dropped. A recent study from the Joslin clinic with patients at durations similar to ours showed mean HbA_1 of 11.0 (23). Our overall glycemic levels appear very much in line with these studies, but absolute comparison is complicated by the different techniques used for measuring glycosylated hemoglobins. It has been shown that wide variation in results exists between methods and between laboratories using the same method (24–27). In general, HbA_1 is expected to be somewhat lower than GHb. American Diabetes Association guidelines place HbA_{1c} cutpoints 2 percentage points lower than those for GHb (28). If this difference holds for our laboratory GHb versus the DCCT HbA_{1c}, glycemic levels in our adolescents aged 13–17 years with median GHb of 11.8 are only slightly higher than in the conventional therapy arm of the DCCT with median HbA_{1c} of about 9.5 and about 2 percentage points higher than in the intensive care arm (19) of the DCCT.

Our region represents a more intense level of diabetes management than is found in some other current studies in the United States. Results of a national survey indicated that only 61 percent of individuals with Type 1 diabetes used two or more injections per day (10), whereas in our sample 95 percent did. Despite this, 38 percent of our population had mean GHb across their duration of greater than 11 percent that was associated with hospitalization rates of over 0.11 per person-year, and 13 percent had GHb levels over 13 percent with a hospitalization rate of 0.20 per person-year. At lower mean GHb, the rate was less than 0.07 per person-year. In addition to underscoring the undesirably high GHb levels in the population, our data on hospitalization rates lend support to American Diabetes Association recommendations that GHb of 13–15 percent is "unacceptable under all normal circumstances" and that "improvement should be attempted" for GHb of 10–11 percent (28, p. 19).

With an average of three insulin injections per day, the Danish group (7, 8) represents a higher intensity of care than do the US population-based cohorts. The Danish mean level of HbA_{1c} is similar to the DCCT result for adolescents in the conventional therapy arm (19) and was deemed unsatisfactory by the investigators. Thus, all the evidence to date indicates that lowering glycosylated hemoglobin to desirable levels is difficult within a wide range of health care systems.

The main features emerging from our longitudinal analysis are a sharp increase in GHb over the first 2 years after diagnosis, with a leveling thereafter, and a peak in the age group 12–15 years. Similar glycemic trends were reported by the studies from Pittsburgh and Denmark (4, 7). However, the Pittsburgh study (4) found the rise in GHb to generally continue up to 4 years of diabetes duration. Recent trends toward more stringent glycemic control may have led to leveling sooner after diagnosis.

The reasons for the observed trends with age and duration remain undefined. Both psychologic (23, 29–31) and physiologic (32–36) risk factors for poor glycemic control have been investigated. Residual beta cell function may explain the lower levels of GHb in the first 2 years of diagnosis (32) as verified by C-peptide levels being measurable in over 90 percent at baseline. However, residual beta cell function does not explain the age patterns we and others have found, as residual function was present in 25–50 percent of adolescents and young adults, but in only 4–6 percent of children. On the other hand, the well-documented insulin resistance (33–36) that develops in puberty may play a role in the peak GHb we observed in the age group 12–15 years and in the higher doses of insulin needed in this age group. Many additional factors may contribute to the pattern of high GHb in adolescence. It has, for example, been proposed that insulin dosage may not keep pace with growth (6).

Most reports (7, 8) have failed to link glycemic control with insulin dosage or frequency of use. On the individual level, there may well be a partial reversal of cause and effect, since persons in poor control may adopt a larger number of injections. We do not, therefore, intend to draw causal inferences, but note that along with a higher number of injections, we did find better dietary compliance and better study compliance in the group with the best glycemic control. It is also notable that in the youngest age groups a larger percentage of subjects are under the care of specialists and parents. On the other hand, glycemic levels across regions and time periods were quite similar despite different levels of diabetes management.

A difference in findings between our study and others pertains to the sex differential in GHb. Other studies have generally found worse control in females (4, 5). However, previous studies have used a considerably cruder breakdown of age, so that typically ages above 12 years have been considered together. Since GHb by no means remains constant in this age group, exact age composition of the adolescent sample can make a difference in results. In Denmark, females were found to have levels of control similar to those of males, but required larger amounts of insulin to maintain these levels (7). Thus, the sex differential may be a result of cultural and health care factors.

Variability in GHb within and between individuals in our study was substantial. We estimate that approximately 30 percent of the variability is due to factors, other than age and duration, that change between test occasion in the same individual and that about 67 percent of the variability may be explained by individual characteristics. This implies a moderate degree of tracking of GHb, which makes a continuing search for individual or health care characteristics that may affect glycemic control somewhat promising. Our study, with its comprehensive description of a large cohort, will continue to search for such factors. Future time trends in population glycemic control are also of great interest. Our description of level and early trends GHb should be useful as a benchmark for comparison with other cohorts with different health care systems and treatment standards.

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