PREDICTORS OF GLUCOSE CONTROL IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

by

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CERTIFICATE OF APPROVAL

This is to certify that the MPH thesis of

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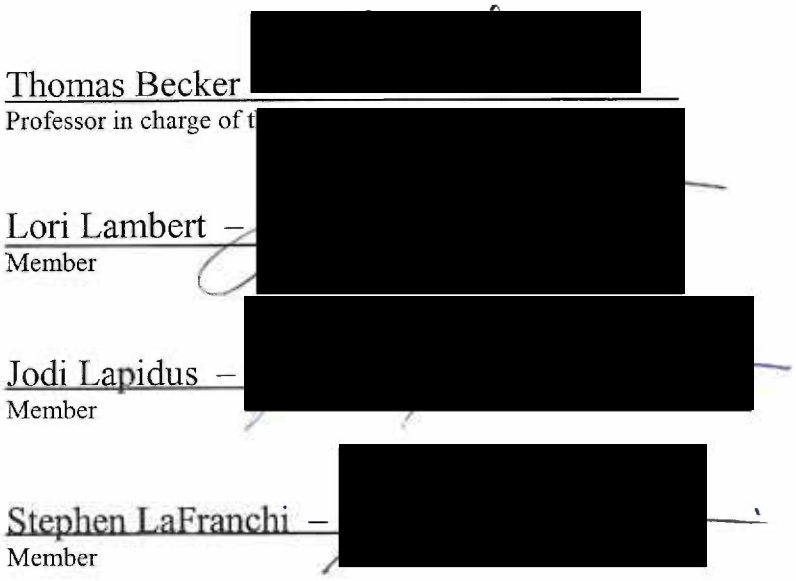

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ABSTRACT

Demographic characteristics, diabetes management strategies, social issues, and economic factors appear to influence glycemic control in children and adolescents with type 1 diabetes mellitus (DM). Identifying the risk factors for poor control may help pediatric diabetologists target patients at high risk of developing diabetes-related complications. We conducted a cross-sectional survey of charts of patients aged 2 – 18 years with type 1 DM treated with multiple daily insulin injections (≤ 4), who had been followed for at least one year at the Doernbecher Diabetes Clinic in Portland Oregon, and had visited the clinic between April and October 2000. Data were abstracted from hospital records and diabetes clinic charts. Associations between potential predictor variables and glycosylated hemoglobin (HbA_{1c}) at the most recent clinic visit were evaluated by multivariate linear regression analysis. Of 269 patients who attended the clinic during the study period, 155 (57.6%) were eligible for inclusion. The mean (± SD) age of the subjects was 12.1 ± 3.9 years, 61.3% were male, and the mean HbA_{1c} value was 9.3 ± 1.3%. In multivariate analysis, patients aged 14 – 18 years had, on average, a HbA_{1c} level 0.6 (95% CI 0.0 – 1.1, P = 0.04) higher than those aged 2 – 8 years. Patients whose parents were either single, separated or divorced had a HbA_{1c} level that was, on average, 0.5 (95% CI 0.0 – 0.9, P = 0.04) higher than those with married parents, and patients with five or more clinic visits in the previous year had a 1.1 higher mean HbA_{1c} level (95% CI 0.2 – 1.2, P = 0.01) than those who attended the clinic three or four times. Among children and adolescents with type 1 DM, poorer metabolic control was associated with age between 14 and 18 years, having parents who were either single,

separated or divorced, and attending diabetes clinic five or more times in the previous year. Physicians caring for patients with these characteristics should target them for more intensive management.

Introduction

1.1 Background

Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia. Defective insulin secretion, insulin action, or a combination of both processes is responsible for this hyperglycemia [1]. There are two distinct types of diabetes. Type 1 diabetes mellitus is most often found in the pediatric population and is caused by destruction of the islet cells of the pancreas (the cells responsible for insulin production). Individuals are said to suffer from type 2 diabetes mellitus if they have insulin resistance alone or in combination with abnormalities of insulin secretion. Type 2 diabetes mellitus is less likely to be diagnosed in the pediatric age group but is increasing among children of Aboriginal, Hispanic, or black origin [1].

Individuals with type 1 diabetes mellitus are dependent on insulin injections to maintain normal blood glucose levels and metabolic homeostasis. Although insulin treatment prolongs the lives of affected individuals, people with diabetes are at risk for severe short- and long-term complications. The short-term complications are related to relative insulin excess or omission, and consist of hypoglycemia and diabetic ketoacidosis. The long-term problems are caused by chronic hyperglycemia and can be defined by their effect on either the microvasculature or the macrovasculature. Microvascular complications include retinopathy, nephropathy, and neuropathy; and macrovascular complications consist of cardiovascular disease, cerebrovascular disease, and peripheral vascular disease. Over time, microvascular damage can lead to blindness, end-stage renal disease requiring dialysis or transplant, and altered sensation in the hands

and feet, while abnormalities of the macrovascular system increase the risk of myocardial infarction, stroke, and amputations.

1.2 Glycosylated hemoglobin (HbA_{1c})

Since the discovery of insulin in 1922, patients with diabetes mellitus are able to avoid the symptoms associated with hyperglycemia. However, they continue to suffer from the complications of the disease. Diabetologists have long suspected that improved glucose control would lead to fewer complications of diabetes, but were unable to show this with any degree of certainty. In 1976 Koenig et al. demonstrated that measurements of the minor hemoglobin, hemoglobin A_{1c} (HbA_{1c}), corresponded with the level of glucose control in the weeks preceding its measurement. These researchers also showed that as improved carbohydrate metabolism was achieved in a group of patients with diabetes mellitus, the HbA_{1c} concentration declined [2]. Hemoglobin A (the most abundant hemoglobin in blood) is modified to glycosylated hemoglobin by the attachment of glucose at a variety of sites on the hemoglobin A (HbA) molecule. The attachment of glucose specifically to the amino terminal valine of the beta chains of the molecule, results in the formation of HbA_{1c} [2]. The group of glycosylated hemoglobins (of which HbA_{1c} is one) are collectively referred to as "total glycosylated hemoglobin" (HbA_1). HbA_{1c} is expressed as a proportion of HbA and ranges between four and six percent in a patient without diabetes. As the glucose level in the blood rises, an increasing proportion of HbA is modified to HbA_{1c} and the percent of HbA_{1c} in the blood rises. Because hemoglobin A is modified to HbA_{1c} throughout the lifecycle of the red blood cell (approximately 90 – 120 days), the concentration of HbA_{1c} appears to be an indicator

of the mean glucose concentration during this period. Further research has demonstrated that HbA_{1c} levels compare favorably to established measures of glucose control. These include mean plasma glucose levels, and percentage of sugar-free urine tests [3]. Because these accepted methods of control evaluation are labor intensive, and physicians' estimates of control based on laboratory and historical data are quite inaccurate [4], HbA_{1c} levels are now used as the standard measure of metabolic control in patients with diabetes.

Although HbA_{1c} levels are useful for comparing the control of patients within a particular center, different methods for HbA_{1c} determination used by different laboratories make it difficult to compare control between centers [5]. This must be kept in mind when reading the diabetes literature. Before changing their practice based on a particular study, clinicians should understand how the different methods of analysis affect the HbA_{1c} level, and how these methods compare to the one used at their center. To standardize the results of studies using HbA_{1c} measurements, it has been suggested that authors use the Diabetes Control and Complications Trial assay method as the reference method [5].

1.3 Diabetes Control and Complications Trial (DCCT)

The Diabetes Control and Complications Trial (DCCT) was a randomized clinical trial that assessed the relationship between glycemic control and the microvascular complications of diabetes mellitus. In this trial, improved control was achieved through intensive treatment of diabetes and close follow up of patients by a multidisciplinary team. Participants in the intensive treatment cohort of the DCCT used three or more

injections of insulin per day, or a continuous subcutaneous insulin infusion, as compared to the conventional treatment cohort who remained on a regimen of two injections per day. The results of the DCCT showed that improved glucose control (as measured by HbA_{1c}), both prevents the onset (1° prevention) and slows the progression (2° intervention) of all microvascular complications: retinopathy, nephropathy, and neuropathy [6]. The outcome of the DCCT has irrevocably changed diabetes management by demanding an increase in the intensity of the approach to diabetes care in order to prevent the complications of the disease. Health care professionals now have the scientific basis on which to recommend that their patients achieve and maintain HbA_{1c} levels close to the values achieved by participants in the intensive treatment arm of the study (7.1% in adults, 8.1% in adolescents) [7].

Since it has been shown that improved control can reduce the risk of complications, researchers have looked for other determinants of control in patients with type 1 diabetes mellitus (besides increasing the intensity of treatment). By outlining and addressing the risk factors for poor control early on in the course of the disease, diabetologists hope to have a large impact on the prevalence of diabetes related complications. The focus of much of the research has therefore been on the pediatric population.

1.4 Factors affecting metabolic control

1.4.1 *Age/puberty*

Diabetologists have long suspected that the level of glucose control is related to the age of children with diabetes. In 1981, Daneman et al. observed a significant linear association between total glycosylated hemoglobin levels (HbA_1) and age, in a sample of 477 children followed at a multidisciplinary diabetes clinic. This relationship was evident until the age of 16 years, and was independent of the duration of diabetes [8].

Between March and August of 1995, 22 pediatric departments from 18 countries participated in a cross-sectional examination of the management and metabolic control of type 1 diabetes mellitus in childhood and adolescence [9]. In this survey of 2837 children, 41% of children younger than 11 years had a HbA_{1c} level less than 8.0% compared with only 29% of adolescents between the ages of 12 and 18 years. The authors hypothesized that this was due to decreased insulin sensitivity in older children because of both enhanced growth hormone secretion and poorer compliance. They further suggested that because of increased involvement of parents in the care of younger children, this group was also more likely to be more compliant with their insulin regimen [9].

Controlled analyses of insulin-stimulated glucose metabolism (using the "hyperinsulinemic-euglycemic clamp method") show that insulin resistance occurs during puberty [10]. During this procedure, patients are given an infusion of insulin at a constant rate. A glucose infusion is also utilized to maintain a steady blood glucose level. The rate of the glucose infusion required to maintain this steady state is used to assess insulin-stimulated glucose metabolism. This rate is expressed as milligrams per square

meter of body surface area per minute [10]. Using a similar method, researchers have also demonstrated that insulin clearance increases during mid-adolescence [11]. Both the aforementioned studies showed that increasing insulin resistance is related, at least in part, to the increasing levels of growth hormone associated with puberty [10, 11].

1.4.2 *Gender*

Mortensen et al. showed that although both males and females require increased insulin doses during puberty, females need higher doses than males [9]. These researchers also demonstrated that females had higher HbA_{1c} values at certain periods during adolescence when compared to males of the same age [12]. Despite the differences in insulin requirements between males and females at adolescence, the relationship between gender and glucose control is not clear. Cross-sectional studies in Belgium and France have failed to show an association between gender and metabolic control as measured by HbA_{1c} [13, 14].

Researchers have attempted to explain the physiological differences between males and females with respect to insulin requirement. Differential growth hormone levels between male and female adolescents appear to influence the insulin-mediated glucose disposal rate. Arslanian et al. used the "clamp method" to demonstrate that this rate is significantly lower in females than in males (26.9 ± 2.1 vs. 47.1 ± 3.7 μmol/kg/min; $P < 0.001$). These females were also shown to have significantly higher growth hormone levels than the males [15].

Pubertal changes in body mass index (BMI, kg/m^2) may also play a role in differential insulin requirements at puberty. The BMI in diabetic children is seen to be

similar in boys and girls until the age of 12 years. After this time, the BMI of girls with diabetes increases more rapidly than that of boys with diabetes. In healthy males and females, the curves representing changes in BMI meet at about 18 years of age. This is not the case in diabetic adolescents. Females with diabetes continue to have a higher BMI than males with diabetes, even after 18 years of age [9]. Since increasing BMI has been found to correlate with increasing insulin resistance, the differences in BMI between males and females at the time of puberty may explain some of the gender difference in insulin requirement and control [11].

1.4.3 *Frequency of diabetes clinic attendance*

Jacobson and colleagues at the Joslin Diabetes Center followed a cohort of 9 – 16 year-old children, with new onset diabetes, for a period of 10 years. They compared children who visited the diabetes clinic on a regular basis, to those who had irregular follow up, defined as missing one year of planned clinic appointments during the second through fourth years after diagnosis. They found that those children in the irregular follow-up group between years two and four, had higher mean (± standard deviation) total glycosylated hemoglobin (HbA_1) values in year one of the study, than those children in the continuous follow-up group (12.2% ± 1.0 vs. 10.8% ± 2.2, $P < 0.05$) [16]. Irregular follow up was also associated with worse glycemic control in years two and three. Although clinically apparent at year four, the difference was not statistically significant. At the seven- and ten-year follow-up visits, no difference in mean HbA_1 values between the two groups was observed. However, ten years after diagnosis, retinopathy was more likely to be found in those children with irregular follow up than in those who attended

clinic continuously in the first four years after diagnosis. Multiple logistic regression analysis showed that HbA_1 was independently associated with the presence of retinopathy at ten years after diagnosis. This suggests that frequent follow up influences the rate of development of complications by its affect on glycemic control [16].

These results were confirmed in a study in 1999, which looked at the relationship between diabetes control (measured by HbA_{1c}), and the annual number of visits to a multidisciplinary diabetes clinic [17]. The study looked at three, one-year time periods and found that children who attended the clinic one or two times per year, had a significantly higher mean HbA_{1c} value, in each year of the study, than those children who had three or four visits per year. This finding was apparent even when the effect of clinic visits was adjusted for age of the patient and the duration of diabetes [17].

1.4.4 *Self-monitoring of blood glucose*

An integral part of the self-management of diabetes involves monitoring blood sugar levels throughout the day, and making appropriate insulin adjustments in response to these values. In the intensive treatment arm of the DCCT, patients tested their blood sugar levels at least four times per day and were encouraged to make insulin adjustments based on these results [7]. In their cross-sectional study of Belgian children and adolescents, Dorchy et al. showed that after two years of diabetes, the number of blood glucose checks per day was negatively correlated with the HbA_{1c} level [13]. The patients in this study were seen approximately nine times per year, allowing for frequent changes of the insulin regimen and extensive education around insulin adjustment. The frequency

of follow up described in this study is not typical of most diabetes programs in North America.

1.4.5 *Insulin injections per day*

Patients in the intensive treatment arm of the DCCT used three or more daily injections or an insulin pump. Since these patients achieved lower HbA_{1c} levels than those in the conventional treatment arm, physicians have assumed that increasing the number of insulin injections per day would be associated with improved metabolic control in their patients [6]. This assumption has not been consistently supported by the literature. In a multicenter cross-sectional study, Mortensen et al. showed that centers with more patients on multiple insulin injections tended to have a lower mean HbA_{1c} than centers with a lower proportion of their patients receiving multiple daily injections. The patients on multiple daily injections did not, however, appear to have lower mean HbA_{1c} values than patients receiving fewer injections at the same diabetes center [12]. This finding suggests, that differing treatment philosophies between centers (not specifically related to the number of insulin injections per day) may account for the differences in control observed.

1.4.6 *Duration of diabetes*

There is conflicting evidence regarding the relationship between duration of diabetes and metabolic control. Earlier studies demonstrated that when the effect of age was taken into account, duration of diabetes was not significantly associated with glucose control [8]. However, recent larger studies have demonstrated an association between

diabetes duration and glucose control. A large cross-sectional French study published in 1998 showed a significant difference between the mean (± standard deviation) duration of diabetes in children with a HbA_{1c} level of < 8% (3.9 ± 2.5 years) compared to those children with a HbA_{1c} of ≥ 8% (5.5 ± 3.7 years) [14].

1.4.7 *Family factors*

Two main theories attempt to explain the relationship between characteristics of patients' families and their diabetic control: the first suggests that stressful family situations lead to an increase in counterregulatory (stress) hormones, which act to raise blood sugar levels; the second stresses the relationship between family support and compliance with the diabetic regimen [18]. In a small pilot study, Lawler et al. demonstrated that adolescents who felt that they received more family support tended to have better metabolic control [18].

Jacobson et al. examined the predictors of irregular versus continuous diabetes clinic attendance. Their study considered the effects of marital status of biological parents, family environment (measured by Moos Family Environment Scale), health insurance status, and social class. The authors showed that patients who came from families with a history of separation or divorce, were more likely to attend clinic irregularly than children who came from intact families [16]. Kaufman et al. replicated these results in a cohort of patients followed in Southern California. In addition, these authors used multivariate analysis to show that the number of clinic visits was independently associated with the degree of metabolic control. Those children who

1.4.9 *Economic factors*

In addition to the expenses related to seeing a physician, patients with diabetes need to purchase expensive medication and supplies. The cost of these supplies, including insulin, syringes, blood testing strips, and blood glucose monitors are often not covered by health insurance companies. Therefore, despite insurance coverage, families with a child with Type 1 diabetes still incur large out-of-pocket health care costs [23]. For families with limited income, this may lead to inadequate access to diabetes care and poorer diabetes control.

1.5 **Rationale**

Multiple factors appear to influence diabetes control. These include demographic characteristics, diabetes-management strategies, social issues, and economic factors. An abundance of literature examines the effect of these factors alone, or in combination with each other. Few studies however, utilized analytic techniques that adjusted for the potential confounding effects of multiple determinants of diabetes control. Even studies that used appropriate statistical techniques did not evaluate all the important determinants of control. Some authors have chosen to dichotomize the outcome variable into "poor" versus "good" control [14]. Not analyzing HbA_{1c} as a continuous variable risks losing substantial information about diabetes control, and therefore missing potentially important effects. In addition, much of the existing literature comes from European countries, which may have different approaches to diabetes management than North America [13]. Information derived from these diverse populations may not be

generalizable to the mainly white population that is treated at our center in Portland, Oregon.

1.6 Objective

To evaluate whether predictors of glucose control in our clinic population are comparable to those reported elsewhere, we conducted a cross-sectional study in a sample of children and adolescents attending a multidisciplinary diabetes clinic in Portland, Oregon.

Methods

2.1 Study setting

Data for this study were obtained from the records of children and adolescents who attend the diabetes clinic at Doernbecher Children's Hospital. At this particular hospital, patients with diabetes are managed by a multidisciplinary team. This strategy is in accordance with the recommendations of the Diabetes Control and Complications Trial (DCCT), as well as with the standards of medical care outlined by the American Diabetes Association [6, 24]. At diagnosis, children are usually admitted to the hospital where they undergo medical treatment as well as extensive diabetes education. During this initial brief hospitalization, children and their families work closely with the pediatric endocrinologist, the certified diabetes educator, and the registered dietician. The medical social worker is also available to identify early stressors that may influence the family's adjustment to the disease. Families are taught how to manage the child's diet, to perform multiple daily glucose checks (capillary blood sample from a finger stick), and to give insulin injections. At the time of discharge, most children are receiving three daily insulin injections and are performing five glucose checks per day. Over the following few weeks, the patients and their families remain in close contact with various members of the team as they learn to adjust to both their diets and their insulin treatment. Families are seen in clinic approximately one month after diagnosis, and at three- to four-month intervals thereafter [25]. A pediatric endocrinologist assesses children at each visit, and yearly meetings are arranged with the diabetes educator, the dietician, and the team psychologist. All members of the team are available during clinic hours in case earlier

intervention is needed. In addition to the input during clinic visits, the diabetes team meets weekly, prior to clinic, to discuss the children that will be attending that week. This allows for anticipation of concerns that may arise at the time of the visit.

2.2 Participants

To be included in the study, patients needed to be between the ages of two and 18 years, have been followed in the clinic for at least one year, and have type 1 diabetes mellitus. Only those patients with diabetes arising from presumed autoimmune destruction of the pancreas were included. To obtain the medical record numbers of children followed at the Doernbecher Children's Hospital diabetes clinic, we reviewed the clinic log for the period from April 1st to October 4th 2000. Since the pediatric diabetes team follows children approximately quarterly, we expected this method to identify a large proportion of all the children followed in the clinic. Two hundred and sixty nine children were seen in the clinic during this time period. A list was generated containing the medical record numbers of these patients. These numbers were used to obtain the children's hospital charts, which were then reviewed by one investigator (SU).

Before embarking on this research project, we obtained approval from the Institutional Review Board at Oregon Health Sciences University (Appendix A).

2.3 Assessment of determinants

All information regarding potential determinants of the HbA_{1c} level at the most recent clinic visit was extracted from the hospital charts of the patients followed in the diabetes clinic. In addition, we examined clinic charts maintained by the endocrine

department to find any information that could not be located in the hospital charts. To minimize measurement error, we designed an electronic database to be used as a data collection tool. This tool consisted of an abbreviated questionnaire with 25 items (including the outcome measure). After a review of the literature and meetings with various members of the diabetes team, we were able to determine exposures that were potentially important in predicting HbA_{1c} levels in this population of patients. Although we recognized the importance of many variables, we were limited by the information that we could realistically expect to find in the patients' charts (Table I).

Table I
Items contained in the questionnaire used for data collection in the *Doernbecher Diabetes Study 2000*

Item	Coding of item
Date of most recent clinic visit	day/month/year
Date of birth	day/month/year
Current Age	years
Date of diagnosis of diabetes	day/month/year
Age at diagnosis of diabetes	years
Duration of diabetes	years
Gender	female, male
HbA_{1c} value at the most recent clinic visit	†
Site of initial diabetes education	OHSU*, other
Initial length of stay in hospital	days
Initial pH	‡
Insulin injections per day at hospital discharge	count
Primary caregiver with diabetes	yes, no
Marital status of biological parents	married, separated, divorced, single, other, unknown
Health insurance	Medicaid, other
Interpreter needed for clinic visits	yes, no
Zip code	alphanumeric text
Other chronic illness	none, asthma, celiac disease, inflammatory bowel disease, other
Prednisone use in previous 3 months	yes, no

Clinic visits in past year	count
Current number of insulin injections/day	0, 1, 2, 3, 4, > 4
Current number of glucose checks/day	0, 1, 2, 3, 4, > 4
Short or rapid acting insulin used	Regular insulin, Lispro insulin, both
Glucagon use in previous 3 months	yes, no
Admissions for diabetic ketoacidosis in previous 12 months	0, 1, 2, > 2

* Oregon Health Sciences University.

† HbA_{1c} and pH were represented as continuous variables with two decimal places. HbA_{1c} is expressed as a percent of HbA (see page 2).

Information regarding prednisone use, health insurance, current number of injections and glucose checks per day, type of insulin used, and requirement for glucagon was assessed at the most recent visit. Data about clinic visits and diabetic ketoacidosis were obtained from reports from the previous year. The remainder of the information was derived from any available source within the hospital or clinic chart. Administrative information such as date of birth, zip code, and health insurance coverage was obtained from registration sheets, while clinical information was usually found in physician and nursing notes. During the data collection process, information linking the patient's medical record number to their study identification number was secured in a locked file.

After reviewing the patients' charts, we found 18 children with chronic illnesses that were not specifically named in our questionnaire. We therefore classified these illnesses as "other." The "other" chronic illnesses found, included depression, mood disorder, attention deficit hyperactivity disorder, developmental delay, epilepsy, absence seizures, testosterone deficiency, and gastritis. We found nine children with caregiver situations that had not previously been defined. These situations were also classified as "other," and included adoption after infancy, foster care, living with a significant other, living with other family members, and death of a parent.

2.4 Assessment of outcome

For the purposes of this study, HbA_{1c} values for each patient were obtained from the chart notes from the most recent clinic visit. If this information was not recorded in the chart, the levels were retrieved from computerized laboratory information at the hospital (n = 3).

HbA_{1c} was assayed with the DCA 2000® + HbA_{1c} System (Bayer, Tarrytown, NY). Since this is the method of analysis used routinely for blood samples of all patients attending the diabetes clinic, the specimens were all analyzed in the same manner. This system allows members of the diabetes team to measure HbA_{1c} levels in six minutes in the clinic setting. A rapid measure enables health professionals to provide feedback about diabetes control before the patient leaves the appointment. The DCA 2000® + HbA_{1c} System uses an immuno-chemical method for the measurement of HbA_{1c} [26]. The reference range for this assay, in individuals without diabetes, has previously been determined to be between 4.3 and 5.7. On testing in various clinic sites, the intraassay coefficients of variation have ranged from 2.2% to 3.3% [26]. In addition, this assay appears to perform favorably when compared with three other methods of laboratory HbA_{1c} measurements (correlation coefficients ranging from 0.97 to 0.99) [26].

2.5 Data management

Data were entered directly into an electronic database (Epi Info 2000, Centers for Disease Control and Prevention, Atlanta, GA). After all the data had been collected they were imported into SPSS version 9.0 for coding and analysis. After the data entry was complete, all documentation linking the patients' medical record numbers to their computer generated identification numbers was destroyed.

2.6 Data analysis

To better define the population of children followed at the Doernbecher diabetes clinic, we examined the demographic and diabetes-related characteristics of our sample.

We then examined these characteristics with respect to diabetes control as measured by HbA_{1c}. Mean HbA_{1c} levels were compared using independent samples t-tests [27] for variables with two categories (gender, glucagon use, diabetic ketoacidosis, prednisone use in the previous three months, current health insurance, site of initial education, parent with diabetes, interpreter needed, injections/day, glucose checks/day), and one-way analysis of variance (ANOVA) [27] for variables with more than two categories (age group, other chronic illness, marital status of biological parents, clinic visits in past year).

Before we embarked on regression model development, we evaluated our outcome variable, HbA_{1c}, to decide how it should be defined. Some consideration was given to dichotomizing the outcome into good versus poor control. This strategy would have allowed us to utilize logistic regression analysis. After discussion with members of the diabetes team, a further review of the literature, and a graphic display of our data we decided that it was more appropriate to define the outcome as a continuous variable. Although HbA_{1c} values above a certain level (depending on the age of the patient) are felt to be alarming, the measurement tends to be used clinically to follow trends and to make interventions based on these trends. Management decisions are seldom influenced solely by a single elevated HbA_{1c} level. In most cases, additional information such as age, pubertal status, social circumstances, and usual level of control is used to aid clinicians in their decisions. For this reason, it is not clinically useful to describe someone as being in good versus bad control based on a single HbA_{1c} measurement. Researchers in the DCCT also noted that the risk of diabetes-related complications increased with increasing HbA_{1c} values, and that the risk of hypoglycemia increased with decreasing HbA_{1c} values. They therefore concluded that no specific target value for HbA_{1c} exists where the risks of

intensive treatment are minimized while the benefits are maximized [6]. In addition, since the HbA_{1c} values were almost normally distributed in our sample, categorizing the outcome into two groups would lead to a loss of potentially important information (Figure 1, page 55). Using a continuous outcome variable allowed us the flexibility to assess factors that were associated with increases or decreases in HbA_{1c} in this particular population.

After we had defined our outcome variable, we proceeded to perform a series of univariate linear regression analyses [28]. We assessed the separate effect of sixteen predictor variables on HbA_{1c} levels in this sample. Fourteen of the predictor variables were categorical while the remaining two were used as continuous variables. The categorical predictor variables included age group (2 – 8 yrs, 9 – 13 yrs, 14 – 18 yrs), gender (female, male), glucagon use in previous three months (no, yes), diabetic ketoacidosis in previous 12 months (no, yes), prednisone use in the previous three months (no, yes), current health insurance (other, Medicaid), site of initial education (OHSU, other), parent with diabetes mellitus (no, yes), interpreter needed for clinic visits (no, yes), other chronic illness (none, hypothyroidism/celiac/asthma, other), marital status of biological parents (married, single/separated/divorced, other), number of clinic visits in past year (≤ 2, 3 – 4, ≥ 5), current injections per day (≤ 2, ≥ 3), and current glucose checks per day (≤ 2, ≥ 3). The continuous predictor variables were age at diagnosis and duration of diabetes. Those variables having a P-value less than or equal to 0.25 on univariate analysis were then considered for inclusion in the multivariate linear regression model [29]. With the exception of gender, which was felt to be clinically

relevant, variables with a P-value greater than 0.05 in the multiple regression analysis were not included in the final model.

After the final model had been established, we used chi-square tests of independence to examine the excluded and included variables for multicollinearity [27]. This allowed us to evaluate why variables that appeared significant using univariate analysis were no longer significant when other variables were included in the regression model. We concluded our data analysis by examining our model for influential observations. Measures of Cook's distance did not reveal any observations that we felt should be excluded [28].

Results

3.1 Patients

At the end of the chart review period, 155 (57.6%) patients remained eligible for inclusion in the study. Of the excluded patients, 40 (14.9%) were diagnosed within a year of their most recent visit and 42 (15.6%) had been followed in the clinic for less than a year or were routinely seen in the outreach clinic where they did not have access to the multidisciplinary team. A further 23 (8.6%) patients were located in error, were not suffering from autoimmune mediated diabetes mellitus, or were using an insulin pump for therapy. We excluded another five (1.9%) patients aged between 19 and 22 years, and were unable to locate the medical records of four (1.5%) patients.

3.2 Demographic and diabetes related patient characteristics

The mean (± standard deviation) age of the subjects was 12.1 ± 3.9 years with 95 (61.3%) male patients (Table II). The mean age at diagnosis of diabetes was 6.3 ± 4.0 years with an average duration of disease of 5.7 ± 3.7 years. Fifty two percent of the patients received their initial diabetes education at OHSU, and 93.5% used 3 or more insulin injections per day. Most subjects visited the clinic between 3 and 4 times in the previous year (75.5%), and 83.9% reported that they were checking their glucose levels 3 or more times per day (Table III).

Table II
Demographic Characteristics of the Study Subjects in the *Doernbecher Diabetes Study 2000*

Characteristic	Value
Age group – no. (%)	
2 – 3 years	37 (23.9)
9 – 13 years	59 (38.1)
14 – 18 years	59 (38.1)
Age – years	
Mean (± SD)	12.1 (± 3.9)
Median	11.9
Range	2.7 – 18.9
Gender – no. (%)	
Female	60 (38.7)
Male	95 (61.3)
Current health insurance – no. (%)	
Other	136 (87.7)
Medicaid	19 (12.3)
Interpreter needed for clinic visits – no. (%)	
No	153 (98.7)
Yes	2 (1.3)
Marital status of biological parents – no (%)	
Married	104 (67.1)
Single/separated/divorced	41 (26.5)
Other*	9 (5.8)
Unknown	1 (0.6)

* Adoption after infancy, foster care, living with a significant other, living with other family members, and death of a parent.

Table III
Diabetes-Related Characteristics of the Study Subjects in the *Doernbecher Diabetes Study 2000*

Characteristic	Value
Age at diagnosis of diabetes mellitus – years	
Mean (± SD)	6.3 (± 4.0)
Median	5.5
Range	0.2 – 16.6
Duration of diabetes mellitus – years	
Mean (± SD)	5.7 (± 3.7)
Median	4.9
Range	1.0 – 16.4
Glucagon use in previous 3 months – no. (%)	
No	152 (98.1)
Yes	3 (2.0)
Diabetic ketoacidosis in previous 12 months – no. (%)	
No	149 (96.1)
Yes	6 (3.9)
Site of initial diabetes mellitus education – no. (%)	
OHSU*	81 (52.3)
Other	74 (47.7)
Parent with diabetes mellitus – no. (%)	
No	139 (89.7)
Yes	15 (9.7)
Unknown	1 (0.6)
Prednisone use in previous 3 months – no. (%)	
No	153 (98.7)
Yes	2 (1.3)
Other chronic illness – no. (%)	
None	127 (81.9)
Hypothyroidism/celiac disease†/asthma	10 (6.5)
Other‡	18 (11.6)

Clinic visits in past year – no. (%)	
≤ 2	29 (18.7)
3 - 4	117 (75.5)
≥ 5	8 (5.2)
Unknown	1 (0.6)
Current insulin injections/day – no. (%)	
≤ 2	10 (6.5)
≥ 3	145 (93.5)
Current glucose checks/day – no. (%)	
≤ 2	23 (14.8)
≥ 3	130 (83.9)
Unknown	2 (1.3)

* Oregon Health Sciences University.

† Celiac disease refers to gluten enteropathy.

‡ Depression, mood disorder, attention deficit hyperactivity disorder, developmental delay, epilepsy, absence seizures, testosterone deficiency, and gastritis.

3.3 HbA_{1c} analysis

The mean (± standard deviation) HbA_{1c} value for this sample of patients was 9.3 ± 1.3%, with the highest average being in the 14 – 18 year age group (9.7 ± 1.5%). There was no significant difference in mean HbA_{1c} level between males and females. Those patients who had had an episode of diabetic ketoacidosis (DKA) in the previous year, had biological parents who were not married, or visited the diabetes clinic 5 or more times in the preceding year had significantly higher HbA_{1c} levels than subjects who had not experienced DKA, had married parents, or attended the clinic between 3 and 4 times in the previous year (Table IV).

Table IV
Mean HbA_{1c} Levels According to Patient Characteristic in the *Doernbecher Diabetes study 2000.*

Characteristic	Mean HbA_{1c}	P-value
Age group		
2 – 8 years	8.9	
9 – 13 years	9.1	
14 – 18 years	9.6	0.01†
Gender		
Female	9.1	
Male	9.4	0.20*
Glucagon use in previous 3 months		
No	9.3	
Yes	9.1	0.78*
Diabetic ketoacidosis in previous year		
No	9.2	
Yes	10.5	0.02*
Prednisone use in previous 3 months		
No	9.3	
Yes	9.4	0.93*
Current health insurance		
Other	9.2	
Medicaid	9.5	0.35*
Site of initial diabetes mellitus education		
OHSU‡	9.3	
Other	9.2	0.72*
Parent with diabetes		
No	9.3	
Yes	9.3	0.92*
Interpreter needed		
No	9.3	
Yes	9.6	0.72*
Other chronic illness		
None	9.2	
Hypothyroidism/celiac disease§/asthma	9.4	
Other¶	9.8	0.11†

Marital status of biological parents		
Married	9.1	
Single/separated/divorced	9.8	
Other**	9.0	0.02†
Clinic visits in past year		
≤ 2	9.6	
3 – 4	9.1	
≥ 5	10.4	0.01†
Current insulin injections/day		
≤ 2	9.8	
≥ 3	9.2	0.22*
Current glucose checks/day		
≤ 2	9.7	
≥ 3	9.2	0.07*

* Independent samples t-test.
† F-test from one-way analysis of variance.
‡ Oregon Health Sciences University.
§ Celiac disease refers to gluten enteropathy.
¶ Depression, mood disorder, attention deficit hyperactivity disorder, developmental delay, epilepsy, absence seizures, testosterone deficiency, and gastritis.
** Adoption after infancy, foster care, living with a significant other, living with other family members, and death of a parent.

3.4 Univariate linear regression analyses

Nine variables reached the level of significance necessary for potential inclusion in the multivariate regression analysis ($P \leq 0.25$). These variables included age group ($P = 0.01$), gender ($P = 0.20$), age at diagnosis of diabetes ($P = 0.03$), DKA in previous 12 months ($P = 0.02$), other chronic illness ($P = 0.04$), marital status of biological parents ($P = 0.01$), number of clinic visits in past year ($P = 0.01$), current insulin injections per day ($P = 0.22$), and current glucose checks per day ($P = 0.07$). When variables were divided into more than two categories, only one of the categories needed to reach significance for the entire variable to be considered for inclusion in the multivariate regression analysis (Table V).

Table V
Potential Determinants of HbA_{1c} Using Univariate Linear Regression, in the *Doernbecher Diabetes Study 2000*

Determinant	β††	95% CI‡‡	P-value
Age group			
2 – 8 years*	0	—	—
9 – 13 years	0.20	-0.32, 0.71	0.46
14 – 18 years	0.72	0.20, 1.23	0.01†
Gender			
Female*	0	—	—
Male	0.27	-0.15, 0.68	0.20†
Age at diagnosis of diabetes mellitus (years)	0.05	0.00, 0.10	0.03†
Duration of diabetes mellitus (years)	0.02	-0.03, 0.08	0.39
Glucagon use in previous 3 months			
No*	0	—	—
Yes	-0.21	-1.68, 1.26	0.78
Diabetic ketoacidosis in previous 12 months			
No*	0	—	—
Yes	1.22	0.19, 2.26	0.02†
Prednisone use in previous 3 months			
No*	0	—	—
Yes	0.08	-1.72, 1.87	0.93
Current health insurance			
Other*	0	—	—
Medicaid	0.29	-0.32, 0.91	0.35
Site of initial diabetes mellitus education			
OHSU*‡	0	—	—
Other	-0.07	-0.48, 0.33	0.72
Parent with diabetes mellitus			
No*	0	—	—
Yes	0.04	-0.65, 0.72	0.92

Interpreter needed for clinic visits			
No*	0	—	—
Yes	0.33	-1.46, 2.12	0.72
Other chronic illness			
None*	0	—	—
Hypothyroidism/celiac disease§/asthma	0.22	-0.60, 1.04	0.60
Other¶	0.66	0.03, 1.30	0.04†
Marital status of biological parents			
Married*	0	—	—
Single/separated/divorced	0.65	0.20, 1.11	0.01†
Other**	-0.12	-0.98, 0.74	0.79
Number of clinic visits in past year			
3 – 4*	0	—	—
≤ 2	0.43	-0.08, 0.94	0.10†
≥ 5	1.26	0.36, 2.16	0.01†
Current insulin injections/day			
≥ 3*	0	—	—
≤ 2	0.51	-0.31, 1.33	0.22†
Current glucose checks/day			
≥ 3*	0	—	—
≤ 2	0.53	-0.03, 1.10	0.07†

*Referent category.
† Below 0.25 level of significance used for initial selection of variables.
‡ Oregon Health Sciences University.
§ Celiac disease refers to gluten enteropathy.
¶ Depression, mood disorder, attention deficit hyperactivity disorder, developmental delay, epilepsy, absence seizures, testosterone deficiency, and gastritis.
** Adoption after infancy, foster care, living with a significant other, living with other family members, and death of a parent.
†† Value of the β coefficient.
‡‡ 95% confidence interval.
Negative values for β coefficients and 95% confidence intervals imply relatively lower HbA_{1c} levels than the referent category.

3.5 **Multivariate linear regression analysis**

Despite the significant association between having an episode of diabetic ketoacidosis (DKA) in the previous 12 months and the level of HbA_{1c}, only six patients in this sample experienced an episode of DKA. Because of the low frequency of this event we chose to exclude this variable from the multivariate regression analysis. Table VI shows those variables that continued to have a significant association with the outcome variable (HbA_{1c}) when they were adjusted for the effects of the other variables in the model. The level of significance used for inclusion in the final model was $P \leq 0.05$. Although the gender variable did not reach this level of significance, we felt that it was clinically important to include it in the final model so that the associations between the other variables and the outcome of interest would be adjusted for gender.

The final linear regression model showed that age group, marital status of biological parents, and the number of clinic visits in the previous year, were associated with the HbA_{1c} level in our patient group (Table VI). The value of the constant in the regression equation was 8.57. This indicates, that males between two and eight years of age with married parents who visited the clinic between three and four times in the previous year had, on average, a HbA_{1c} value of 8.57%. Values of β coefficients for each variable are added to the value of the constant to give a predicted HbA_{1c} level for any particular patient. On average, patients between 14 and 18 years of age had a HbA_{1c} value 0.56 higher than children between the ages of two and eight years of age. Patients with parents who were single, separated, or divorced had a HbA_{1c} value 0.47 higher than patients with married parents. Those patients who visited the clinic five or more times in the previous year showed an increase in their HbA_{1c} levels of 1.11 as

compared to patients who were seen between three and four times. Finally, we noted a tendency for patients who attended the clinic two or fewer times during the previous year to have a HbA1c level of 0.46 higher than those who attended clinic between three and four times (Table VI).

The final multivariate linear regression model accounted for 11% of the variability in HbA_{1c} values between patients ($aR^2 = 0.11$).

Table VI
Determinants of HbA_{1c} in Children and Adolescents with Type 1 Diabetes Mellitus, Using Multivariate Linear Regression, in the *Doernbecher Diabetes Study 2000.*

Determinant	β‡	95% CI§	P-value
Constant	8.57	8.07, 9.07	0.00
Age group			
2 – 8 years*	0	—	—
9 – 13 years	0.20	-0.31, 0.71	0.44
14 – 18 years	0.56	0.03, 1.08	0.04
Gender			
Female*	0	—	—
Male	0.26	-0.14, 0.67	0.20
Marital status of biological parents			
Married*	0	—	—
Single/separated/divorced	0.47	0.02, 0.93	0.04
Other†	-0.26	-1.10, 0.58	0.54
Clinic visits in past year			
3 – 4*	0	—	—
≤ 2	0.46	-0.05, 0.97	0.07
≥ 5	1.11	0.23, 1.20	0.01

* Referent category.
† Adoption after infancy, foster care, living with a significant other, living with other family members, and death of a parent.
‡ Value of the β coefficient.
§ 95% confidence Interval.
Final model is adjusted for all variables shown ($aR^2 = 0.11$, $F = 3.54$, $P = 0.002$).
Negative values for β coefficients and 95% confidence intervals imply relatively lower HbA_{1c} levels than the referent category.

When adjusted for the effects of the above variables (with the addition of gender), current glucose checks per day, other chronic illness, and age at diagnosis of diabetes were no longer significantly associated with the outcome. We looked for evidence of multicollinearity to explain this phenomenon, and found that current glucose checks per day was significantly associated with the marital status of the biological parents ($P < 0.001$), and that the presence of another chronic illness was significantly associated with the number of clinic visits in the previous year ($P = 0.05$) (Tables VII and VIII).

Table VII
Evaluation of the Association Between the Variables "Current Glucose Checks per Day" and "Marital Status of Biological Parents", Using Chi-Square Test of Independence, in the *Doernbecher Diabetes Study 2000*

			Marital status of biological parents		
			Married	**Divorced/ separated/ single**	**Other***
Current glucose checks/day	**≤ 2**	**Count**	7	14	2
		Percent†	30.4%	60.9%	8.7%
	≥ 3	**Count**	97	25	7
		Percent†	75.2%	19.4%	5.4%

* Adoption after infancy, foster care, living with a significant other, living with other family members, and death of a parent.
† Percentages given are for row totals.
Pearson chi-square = 19.2, $P < 0.001$.

Table VIII
Evaluation of the association Between the Variables "Other Chronic Illness" and "Visits to Clinic in the Past Year", Using Chi Square Test of Independence, in the *Doernbecher Diabetes Study 2000*

			Visits to clinic in past year		
			≤ 2	3 – 4	≥ 5
Other chronic illness	None	Count	21	101	4
		Percent‡	16.7%	80.2%	3.2%
	Hypothyroidism/ celiac disease*/asthma	Count	3	6	1
		Percent‡	30.0%	60.0%	10%
	Other†	Count	5	10	3
		Percent‡	27.8%	55.6%	16.7%

* Celiac disease refers to gluten enteropathy.
† Depression, mood disorder, attention deficit hyperactivity disorder, developmental delay, epilepsy, absence seizures, testosterone deficiency, and gastritis.
‡ Percentages given are for row totals.
Pearson chi-square = 9.4, P = 0.05.

Discussion

4.1 Summary of the results

Our study showed that adolescents between the ages of 14 and 18 years were in poorer metabolic control than children between the ages of 2 and 8 years. Children with married parents were in better control than children of single, separated, or divorced parents, and children who attended the diabetes clinic five or more times in the previous year were in worse control than children who had three or four visits. We also noted a tendency for children who visited the clinic two or fewer times in the previous year to have worse control than those who had three or four visits. Since we included gender in the final model, the significant findings are adjusted for the effect of gender. We did not find an independent association between gender, duration of diabetes, number of glucose checks per day, or insulin regimen with the HbA_{1c} level at the most recent clinic visit.

4.2 Interpretation of the results

In our study, increasing age was associated with worse metabolic control. This is consistent with the findings of Daneman et al. [8] and Mortensen et al. [9], and is likely due to the increasing insulin resistance noted during the pubertal years [10, 11]. We did not record information about insulin dose and were, therefore, unable to assess the effect of increasing age on insulin dose requirements. In describing the Belgian experience, Dorchy et al. did not find a relationship between age and metabolic control. Their study did, however, show an increase in insulin requirement at puberty [13]. The children in the Belgian study visited the clinic approximately nine times per year. It is possible that

despite increasing insulin resistance, insulin doses were adjusted frequently enough to prevent increases in HbA_{1c}.

We categorized age into groups that allowed us to examine the effect of (1) different stages of pubertal development and (2) different levels of responsibility for diabetes management. Between the ages of 14 and 18 years, most patients are expected to assume responsibility for their own diabetes care. During this time, many parents stop supervising blood testing, insulin adjustment, and injections [30]. The decline in glucose control noted in our sample of older adolescents is not surprising, since the changing hormonal milieu of these adolescents already places them at risk for higher HbA_{1c} levels.

Our results did not suggest an association between gender and glucose control. Others who found an association attributed it to a higher level of insulin resistance in females compared to males of the same age. Females have a higher body mass index (BMI) during puberty than males. This may be responsible for the relatively higher insulin resistance seen in females as well as their higher insulin requirement at puberty [11]. We did not assess the difference in insulin requirement between males and females in our study. In addition, because we did not record patient height and weight, we were unable to draw any conclusions about the effect of BMI on metabolic control or insulin requirement.

To assess whether gender differences in HbA_{1c} exist during puberty, we conducted a separate analysis of adolescents between 14 and 18 years. We found no significant differences in HbA_{1c} values between males and females. However, because of a low number of patients in the 14 – 18 year age group, and increased variability of the

HbA_{1c} values among these adolescents, it may be difficult to demonstrate a significant difference between the genders, even if one does exist (Figure 2).

In our sample, patients who attended the clinic five or more times in the previous year had worse HbA_{1c} levels than those who had three or four clinic visits. There is no clinical reason to hypothesize that increasing the frequency of clinic visits will lead to worse control. Rather, the reason for this association is probably the practice of following those in poor control more closely. More frequent visits may, therefore, be a marker of poor control, and not a cause of it. There was also a tendency for those patients who attended the clinic two or fewer times in the previous year to have worse control than those who had quarterly visits. Kaufman et al. also described this relationship in a sample of children followed at diabetes centers in Southern California [17]. It is not clear what component of the clinic visit accounts for the improvement in metabolic control. Presumably it is related to more frequent adjustments of insulin regimens, an increase in the number of opportunities for education and motivation, and the ability to assess and address compliance issues more regularly.

We found an association between the number of clinic visits in the previous year and the presence of another chronic illness. Specifically, those patients classified as having an "other" illness were more likely to have attended the clinic five or more times or two or fewer times in the previous year than those patients without another illness (16.7% vs. 3.2%, 27.8% vs. 16.7%) (Table VIII). The "other" category of the other chronic illness variable consists of patients diagnosed with depression, mood disorder, attention deficit hyperactivity disorder, developmental delay, epilepsy, absence seizures, testosterone deficiency, and gastritis. Most of these patients have a psychiatric diagnosis.

We believe that the high prevalence of psychiatric conditions among this group predisposes them to the conditions that lead to poorer metabolic control. This may explain why a higher proportion of this group was seen five or more times in the previous year.

When assessed by univariate linear regression analysis [28], current glucose checks per day and glucose control were weakly associated (P = 0.07). In our population, patients performing two or fewer blood glucose checks were in worse control than those testing three or more times per day. When we placed current glucose checks per day in a model with marital status of biological parents, glucose checks per day was no longer associated with the outcome (P = 0.72). On further investigation, we noted that glucose checks per day was significantly associated with the marital status of the biological parents (Table VII). In our sample, only 30.4% of the patients who checked their blood sugars two or fewer times per day had married parents, compared with 75.2% of those patients who did three or more glucose checks per day (Table VII). Other studies have demonstrated better control in children who perform more frequent home blood glucose monitoring [13, 14], but we are not aware of any previous research that shows the association between marital status of the parents and the number of blood glucose checks per day. It should be kept in mind that simply performing multiple blood glucose checks per day is unlikely to improve glucose control. Centers that have shown an improvement in HbA_{1c} values with more frequent home blood glucose monitoring have also taught their patients how to recognize trends in their results, and to make appropriate insulin adjustments [6]. Although the association of this variable with the level of glucose control has been extensively evaluated, it may not really represent how well the

individual is making insulin adjustments, but may rather be a marker for compliance in general.

In this population of patients, no association was observed between the number of insulin injections per day and the degree of metabolic control. Two possible explanations for this finding exist: First, since the publication of the findings of the DCCT, most patients with diabetes have been treated with at least three insulin injections per day. In our sample, only ten patients (6.5%) remained on two or fewer injections per day. Because the majority of patients were receiving three injections per day, we would have needed many more patients to detect an effect of injection number on glucose control. Second, as other authors have suggested, other areas of intensive management, not specifically related to injection number, may influence metabolic control.

The marital status of the biological parents was an important predictor of glucose control in our sample. Patients of parents who were single, separated, or divorced had a HbA_{1c} level that was, on average, 0.5 higher than those patients whose parents were married (adjusted for age, gender, and number of clinic visits in previous year). Researchers have suggested that stressful family events may lead to higher blood sugar levels through increased counterregulatory hormonal responses. Others feel that less family support decreases compliance with the diabetic routine [18]. Although we did demonstrate an association between marital status and one marker of compliance (glucose checks per day), we were not able to show an association between marital status and the number of clinic visits in the previous year (Pearson Chi-square = 2.01, P = 0.74). Other authors have demonstrated this association [16, 17]. We did not directly measure family stressors or family cohesiveness in this study, but think it quite likely that these

factors influence glucose control directly, or through their association with compliance and other aspects of diabetes management.

We did not administer any psychological tests to our study population. We can therefore not make any comment about the effect of psychological characteristics on metabolic control. However, when we considered the "other" group among the children with additional chronic illnesses we saw some interesting trends. The patients with "other" illnesses had a mean (± standard deviation) HbA_{1c} value of 9.8 ± 1.8% compared to those patients without another chronic illness who had a mean (± standard deviation) HbA_{1c} of 9.2 ± 1.2%. We can hypothesize that the high prevalence of psychiatric diagnoses among this group of patients is responsible for the poorer metabolic control observed.

In our study, no association between health insurance status and HbA_{1c} value was observed. However, since all patients attending the clinic had some form of health insurance at the time of the visit, it was not possible to assess the effect of having no insurance on the outcome. During the course of the chart review, we identified many cases where care had been discontinued with loss of insurance, and was later reestablished. We were not able to objectively measure interruptions in care, and could therefore not determine whether they had an influence on diabetes control. However, being insured by Medicaid did not appear to limit access to this particular multidisciplinary diabetes clinic. A Pearson Chi-square analysis of the association between the number of clinic visits in the previous year and the type of health insurance coverage was not statistically significant (Pearson Chi-square = 2.30, P = 0.32).

There was likely some error in coding of insurance status. Some families that fall below a certain income level are eligible for Medicaid and are assigned to a local Health Maintenance Organization. The insurance information of these patients would indicate a Health Maintenance Organization as providing medical coverage and would not mention Medicaid or any of the other insurance programs that derive funding from Medicaid e.g. Oregon Health Plan. When reviewing the charts of these patients, it is likely that many patients receiving Medicaid were coded as having "other" insurance. If a difference existed between the HbA_{1c} values of patients receiving Medicaid and those receiving all other types of health insurance, this error would bias the results toward showing no difference between the groups.

4.3 **Limitations of the study**

Because the present study had a cross-sectional design and utilized retrospectively gathered data, it was subject to numerous sources of error. Even though we attempted to limit measurement error by using a predesigned data collection tool, there may have been inaccuracies in the original documentation in the medical records. Physicians and nurses at the diabetes clinic do not use a specific questionnaire for each visit; rather they adapt their inquiries to the perceived needs of each patient. Some data were missing or very difficult to find. This was especially true for information about marital status of parents, additional chronic illnesses, and need for an interpreter. Changes in family situations and the development of illnesses since the time of diagnosis were seldom documented and therefore likely under-reported.

The patient and his or her family provide most of the information for the diabetes team. Although members of the diabetes team attempt to review the diabetes record maintained by the child, it is occasionally unavailable or inaccurate. The measurement error introduced by these patient reports is therefore quite considerable. This is especially true in the adolescent population where parents are no longer involved in the patients' diabetes management and diabetes records are seldom maintained. The multiple sources of measurement error in a retrospective study need to be remembered when interpreting the results of this study. Non-differential misclassification, which has likely occurred in this study, will most often cause a result to be biased toward the null hypothesis [31]. This source of bias may have led us to miss potentially important associations.

After exclusions, only 155 (57.6%) of the original 269 patients remained eligible for the study. This large reduction in our study sample decreased our power to detect small associations between the predictor variables and the HbA_{1c} level. Since this model was intended for descriptive, hypothesis-generating purposes, we elected to continue with the study despite the small sample size.

Because of variations in the detail of patient records we were unable to reliably document pubertal status, and insulin dosages. In addition, we did not record information about height and weight, which would have allowed for a BMI calculation. This information would have been extremely useful when examining the effects of age, gender, and pubertal development on insulin resistance and glucose control. Zachrisson et al. showed that adolescents with Tanner stage 1 pubertal development tended to have lower HbA_{1c} levels than those with Tanner stage 5 pubertal development [32]. It would

have been interesting to have assessed the effect of pubertal development in our patient population.

Finally, the individual who performed the chart review was the same individual who reviewed the literature on this area of research. This individual was aware of the well-recognized associations prior to abstracting the data. Despite adherence to a predesigned data collection procedure, the absence of blinding may have introduced a further source of bias into the study.

4.4 Importance of the study findings

Our study has shown that many of the same variables that are associated with metabolic control in the literature, are relevant in our clinic population as well. The advantage of our study is that the effect of these predictor variables was assessed using multivariate statistical techniques. Multivariate linear regression analysis allowed us to adjust for the effect of potential confounding variables when considering the association between candidate predictor variables and the outcome of interest. We showed that older age, marital disruption, and more frequent clinic attendance were independently associated with metabolic control. We also showed a tendency for less frequent clinic attendance to be associated with control. Identifying patients at risk will allow the diabetes team to intervene before deteriorations in metabolic control occur.

Our study suggests that although a difficult age group to engage, adolescents who are assuming responsibility for their diabetes management need to be followed especially closely. They should receive individualized diabetes education and be in more frequent contact with the diabetes team. Members of the diabetes team need to be aware of

changing family situations and to identify patients who require extra support in the management of their diabetes during particularly stressful times. Regular clinic attendance is clearly an important component of intensive diabetes management, and children and adolescents should be assessed at least three to four times per year. Strategies must be developed to improve accessibility to the clinic (e.g. organized transportation, shorter waiting times) and to identify patients who frequently miss appointments.

4.5 Recommendations and directions for further research

Our study identified some important risk factors for poor metabolic control in children and adolescents with Type 1 diabetes mellitus. Nevertheless, our final multivariate linear regression model only accounted for 11% of the variability in HbA_{1c} values seen in the diabetes clinic at Doernbecher Children's Hospital (adjusted R^2 = 0.11). Studies that have accounted for a larger proportion of the variability have assessed the effect of many more variables in a much larger sample of children [14]. Further research in this area would be easier to perform if a standardized data collection and documentation system (database) were in place. The completion of a standardized questionnaire at each clinic visit would provide the diabetes team with information about important demographic and diabetes-related characteristics. Entering information into a database would also limit the amount of measurement error, which is a large limitation of the present study. Since there are no specific guidelines for the questions asked at the clinic visits, not all charts contained the same information. This limited the number of variables available for study and the quality of the information obtained. Having

structured questionnaires for each visit, and entering this information into an electronic database, would improve the quantity and the quality of the data used for further studies. Additional information that may be recorded in the database should include insulin dose, height, weight, pubertal status, and blood pressure at each visit. Indicators of socioeconomic status such as parental education and family income would provide additional useful information. Results of routine screening tests for retinopathy and nephropathy should also be entered into the database to assess the relationship between control and complications in a younger population than that studied in the DCCT.

Most of the large studies focusing on predictors of diabetes control have been performed in Europe. Information obtained from these studies may therefore not be completely generalizable to our population. Encouraging all diabetes clinics to make use of a database would enable us to perform large multicenter studies in North America.

Evaluating the control of children and adolescents using continuous subcutaneous glucose infusions was beyond the scope of this study. Future research should include this population of patients both to evaluate their level of control, and to examine whether predictors of control in this group are the same as those in patients using multiple daily injections. A diabetes database would enable us to compare the demographic and diabetes-related characteristics of children using an insulin pump to those receiving multiple daily injections.

Conclusion

We performed a cross-sectional study to examine the predictors of control of diabetes in a sample of children and adolescents followed at Doernbecher Children's Hospital in Portland, Oregon. Despite the potential limitations of this study, we have shown that adolescents between the ages of 14 and 18 years were in poorer metabolic control than children between the ages of 2 and 8 years. Children with married parents were in better control than children of single, separated, or divorced parents, and children who attended the diabetes clinic five or more times in the previous year were in worse control than children who had three or four visits. We also observed a tendency for children who visited the clinic two or fewer times in the previous year to have worse control than those who had three to four visits. No independent association was noted between gender, duration of diabetes, number of glucose checks per day, or insulin regimen with the HbA_{1c} level at the most recent clinic visit. We believe that health professionals who care for patients at higher risk for poor control, should follow these children on a regular basis and be more vigilant about ensuring clinic attendance and compliance with the diabetic regimen. The diabetes team must be prepared to provide these patients with extra medical, educational, and social work support during potentially stressful periods. Further research would be facilitated by maintaining a detailed clinical database for diabetes care.

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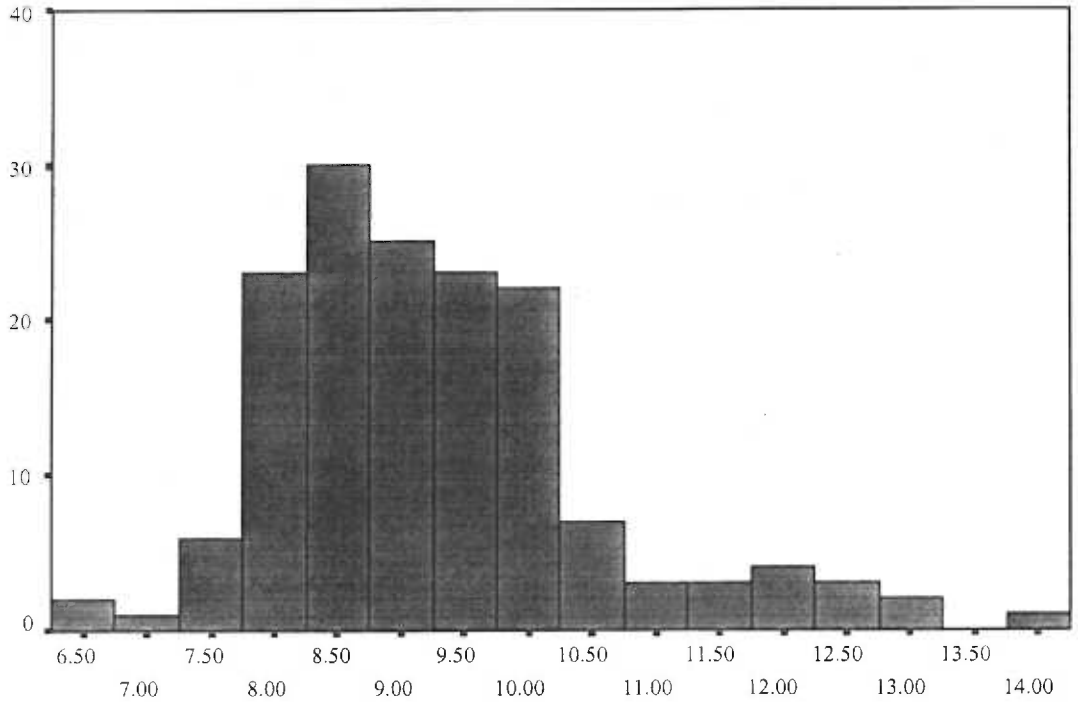
FIGURES

Figure 1

Distribution of HbA_{1c} Values in the *Doernbecher Diabetes Study 2000*

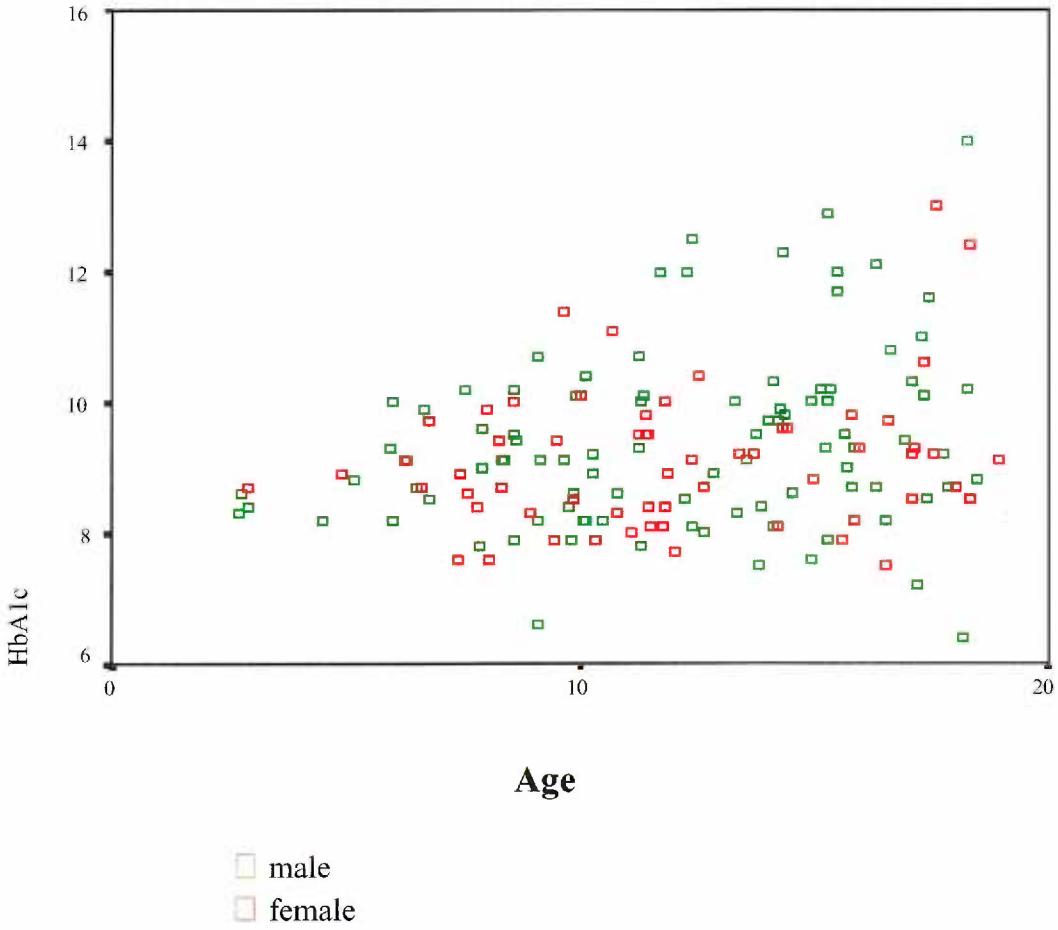
N = 155, mean = 9.3%, SD = 1.27



HbA_{1c} at Most Recent Clinic Visit

Figure 2

HbA_{1c} Values by Age and Gender



APPENDICES

Appendix A

Institutional Review Board Approval

OREGON HEALTH SCIENCES UNIVERSITY
Office of Compliance & Assurance, L106 (503) 494-7887

MEMO

Date: October 2, 2000

To: *Thomas M. Becker, MD, CB669* Stacey Urbach

From: Gary T. Chiodo, DMD, Chair Institutional Review Board, L106
Leslie Bevan, PhD, Director, Compliance & Assurance, L106
Charlotte Shupert, PhD, Compliance Manager, L106

Subject: ***6168 EXP***
Predictors of diabetes control in children and adolescents with type I diabetes mellitus.

Initial Study
Review Communication

[■] The protocol/consent form was approved by the IRB for **one year** effective **10/02/00** .

[ ] The protocol/consent form was reviewed by the IRB on_____; it will be approved by the IRB upon completion of the recommended changes/revisions (see attached).[2] The changes/revisions are due to the RSO by _____. **If the recommended changes are not received within 60 days, your study will be returned to you. At that point, resubmission will require another review.**

[ ] The protocol/consent form was reviewed by the IRB on _____ and was

[ ] deferred[2]

[ ] disapproved[2]

[ ] This study meets the criteria established for waiver of consent. No consent form is required.

[ ] The above study involves only discarded tissues/samples that do not include *identifiable private data/information obtained in a form associable with an individual*. Therefore, the study meets the criteria for nonhuman subject and is exempt from IRB review.

[■] This above study meets the criteria for EXPEDITED IRB review based on category # 5 .

[2] see attached IRB REVIEW SUMMARY