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The utility of hemoglobin A1c at diagnosis for prediction of future glycemic control in children with type 1 diabetes

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Abstract

Introduction—We evaluated the relationships of hemoglobin A1c (A1c) at diagnosis of type 1 diabetes (T1DM) to future glycemic control and to a series of clinical variables in children with T1DM.

Materials and methods—Patients <18 years old diagnosed with T1DM during a one year period who had an A1c at diagnosis and at least one follow-up visit at our center were eligible for inclusion. Baseline variables examined included age, race, gender, symptom duration, admission acuity, anthropometrics, bicarbonate, and A1c. Annual anthropometric and A1c data were also obtained from clinic visits through 4 years after diagnosis.

Results—We identified 120 children (53 males). Mean age at diagnosis was 7.6 ± 3.9 years. Mean A1c at diagnosis was $10.9 \pm 1.9\%$. A1c at diagnosis correlated with age at diagnosis, symptom duration, and A1c at 3-years, with trends towards correlations at 6 weeks and 4 years. A1c at 1 year correlated highly with A1c at subsequent visits. No other baseline variables correlated with subsequent glycemic control.

Conclusions—In children with newly diagnosed diabetes, A1cs at diagnosis and one year post diagnosis are related to subsequent glycemic control. Children with high A1cs particularly at one year post diagnosis may benefit from targeted intensification of resources.

Keywords

Type 1 diabetes mellitus; Hemoglobin A1c; Glycemic control; Children; Adolescents

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Conflict of interest

The authors declare that they have no conflict of interest.

1. Introduction

Type 1 diabetes mellitus (DM) has significant long term consequences, including microvascular and macrovascular morbidities [1,2]. Available data indicate that the risk of long-term complications is decreased with stringent glycemic control [1,2]. Factors that influence glycemic control in children include adherence to therapy, parenting styles [3], race [4], family socioeconomic status, and mental health [5]. Hemoglobin A1c (A1c) is used clinically as a reliable measurement of glycemic control over the preceding 2–3 month period. Current ADA guidelines call for children with diabetes to achieve a target A1c <8.5% but >7.5% for children 0–6 years of age, <8% for those 7–13 years of age and <7.5% for those over 13 [6].

A few studies have examined characteristics of pediatric diabetic populations at diagnosis. These include the effects of children's ages on the time to diagnosis [7], descriptions of symptoms [8], and biochemistries at diagnosis [7,8]. A1c has also been utilized as an indicator of diabetes duration prior to diagnosis [9]. However, there remains little investigation of which, if any, characteristics at diagnosis predict future glycemic control. In this study, we explored the relationships of A1c at diagnosis to a series of clinical variables. We then examined correlations of these baseline variables with future glycemic control.

2. Methods

Following institutional review board approval, we queried our outpatient diabetes clinical database and extracted all patients diagnosed with type 1 diabetes in 2003 who were hospitalized at our urban, tertiary care children's hospital. We then selected all patients less than 18 years of age with at least one follow up visit through our hospital clinics. The diagnosis of type 1 diabetes was based upon clinical criteria and positive autoantibodies at diagnosis (GAD, islet cell, and/or insulin). Children were excluded from analysis if they either did not have an A1c recorded at diagnosis or did not have subsequent follow up at our facility.

Using both electronic medical records and review of inpatient and outpatient paper charts we extracted the following clinical variables at the time of diagnosis: age, gender, race, duration of symptoms reported by caretakers to the admitting physicians, location of first admission (intensive care unit (ICU) or general pediatric unit), anthropometric data (height, weight, body mass index (BMI)), serum bicarbonate, A1c, and discharge insulin regimen. We collected insurance type (Medicaid vs. private insurance vs. self pay) as a marker for socioeconomic status (SES). We also extracted anthropometric and A1c data from clinic visits at 6 weeks, 1, 2, 3, and 4 years after diagnosis. Follow-up visits were deemed adequate to be assessed at the specified time interval if the visit date was 10–14 months from the anniversary of the diagnosis of diabetes.

A1c was measured at our facility using DCA 2000 point of care sampling (Bayer Diagnostics) for clinic visits at the 6 week, 1 year, 2 year, 3 year, and 4 year follow up intervals. A1cs obtained at other facilities prior to transfer to our hospital at the time of diagnosis were sometimes measured using other assays. Because the upper limit of the A1c

assay using the DCA 2000 is 14%, any outside A1cs >14% were converted to 14.1 for subsequent analyses.

2.1. Statistical analysis

Statistics were performed using SPSS software version 17.0. Mean, standard deviation (SD), and range were calculated for age and A1c at every interval. Two way ANOVAs were used for comparison of multiple groups. In general, results were considered to be statistically significant if $p < 0.05$. A Bonferroni correction with Sidak's adjustment was done to account for multiple comparisons of A1cs over time [10] to reduce the probabilities of either type I or type II errors. BMI z-scores were calculated from height, weight, and age using a web based program: <http://stokes.chop.edu/web/zscore>.

3. Results

We identified 133 children, aged 1–17 years, who were hospitalized at our facility during 2003 with a new diagnosis of type 1 DM. Of these, 122 had an available A1c. One hundred and twenty had at least one follow up visit at our facility. Follow up data were available for 119 children at the 6 week and 1-year time points. At the 2- and 3-year time points, there were 116 and 112 children with follow up data, respectively. At the 4-year follow up visit, 107 children had data.

3.1. Characteristics at diagnosis

At the time of diagnosis, the mean A1c was $10.9 \pm 1.9\%$ (range 6.7–14.1%). Other patient characteristics (gender, race, symptom duration, BMI z-scores, and serum bicarbonate) are reported in Table 1. Thirty patients, who presented with diabetic ketoacidosis, were admitted to the ICU; the rest were admitted to the general pediatric unit. Higher A1cs at diagnosis were found in children who were older (Fig. 1A), had a longer reported duration of symptoms prior to diagnosis (Fig. 1B), and had a lower BMI z-score at diagnosis ($r = -0.3$, $p = 0.01$). Although they were more acutely ill, patients admitted to the ICU did not have higher A1cs at diagnosis than those admitted to the general pediatric floor (mean A1c for ICU-admitted $11.6 \pm 1.6\%$; for floor-admitted $10.8 \pm 2.0\%$, $p = 0.249$). There was also no correlation between the severity of acidosis (as indicated by serum bicarbonate) and A1c at diagnosis, $p = 0.56$. A1c at diagnosis did not vary by gender ($p = 0.55$) or race ($p = 0.88$). We did not see a relationship between insurance type and A1c at diagnosis. All children were discharged from the hospital on regimens of injected insulin using a combination of NPH and insulin aspart.

3.2. Longitudinal data

A1c values from diagnosis were compared to A1c values at follow-up intervals, and A1cs at the follow up intervals were compared to each other (Table 2). To account for multiple comparisons, with a mean correlation between A1cs of 0.24, only p -values of < 0.016 were considered significant [10]. As would be expected, A1c at diagnosis trended towards a correlation with A1c at the 6 week follow up ($r = 0.35$, $p = 0.02$). A1c at the 1- and 2-year follow up visit did not correlate with A1c at diagnosis. A1c at the 3-year follow up

correlated with A1c at diagnosis, $r = 0.29$, $p < 0.01$, and at the 4-year follow up, the trend continued but was not significant, $r = 0.18$, $p = 0.07$.

Mean A1c values were 8.7 ± 1.2 at 1 year, 8.5 ± 1.2 at 2 years, 8.7 ± 1.5 at 3 years, and 8.7 ± 1.4 at 4 years of note, A1c at the 1 year follow up was significantly correlated to A1c at 2 and 4 year intervals ($r = 0.61$, $p < 0.001$ and $r = 0.31$, $p < 0.001$ respectively) and trended towards correlation at the 3 year interval ($r = 0.18$, $p = 0.05$) (Table 2).

At the 4-year interval, 107 children of our original cohort (41% male) were still followed at our center and 100 had an A1c available. Twenty six percent of these were in good control for age based on ADA guidelines [6]. Fifty-six children were on carbohydrate to insulin ratios, 40 were on insulin pump therapy, and 11 were on sliding scales with long acting insulin and fixed mealtime carbohydrates. Those who were on pump therapy had a lower A1c at diagnosis, ($10.5 \pm 1.8\%$ vs. $11.3 \pm 1.8\%$, $p = 0.02$) and also showed a trend towards better glycemic control, with a lower A1c at the 4-year follow up ($8.4 \pm 1.4\%$ (range 5.8–14.0) vs. $9.0 \pm 1.5\%$ (range 5.8–14.0), $p = 0.07$), compared to those not on pump therapy. A1c at the 4-year follow up was not predicted by gender, age at diagnosis, bicarbonate at diagnosis, ICU admission at diagnosis, or symptom duration at diagnosis. There was no relationship between insurance type at diagnosis and A1c at any follow up interval.

We also examined whether those children in the highest and lowest A1c quartiles at 1 year remained in those quartiles over time. At the 1 year interval, the 75% for A1c was 9.7% and the 25% was 8.1%. Twenty-three patients had A1c values of 9.7%. Of these, only three achieved A1c values of 8.0% at the 4 year mark. Mean A1c at the 4 year interval in this poorly controlled group was $9.5 \pm 1.5\%$. Twenty-seven patients had A1c values 8.1 at one year, indicating good control. At four years, mean A1c in this group was $8.3 \pm 1.7\%$. Fifteen children in this group had an A1c of 8.0%.

BMI z-score at diagnosis was significantly correlated with BMI z-score at each follow up interval (at 6 weeks -0.4 ± 1.59 , $r = 0.85$, $p < 0.0001$; at 1 year 0.72 ± 0.93 , $r = 0.68$, $p < 0.001$; at 2 years 0.74 ± 0.9 , $r = 0.67$, $p < 0.001$; at 3 years 0.61 ± 1.25 , $r = 0.67$, $p < 0.001$; at 4 years 0.66 ± 0.86 , $r = 0.73$, $p < 0.001$).

4. Discussion

A1c values reflect average glycemia over the preceding few months and are related to the development of long-term complications [11]. Optimizing A1c while minimizing hypoglycemia is a primary aim of therapeutic interventions in persons with diabetes. Finding factors at diagnosis or early in the disease course that predict subsequent glycemic control is important for enabling early targeting of limited resources to those patients most at risk for future complications.

In our cohort, only older age and longer duration of symptoms correlated with higher A1c at diagnosis, similar to a previous study [12]. A1c at diagnosis was also significantly correlated with A1c at 3-year follow up and showed a trend towards correlation at 4-year follow up. These results indicate that A1c at diagnosis has some limited predictive value. A1c at 1 year was more highly predictive of future glycemic control. The 1-year A1c showed significant

correlations to the 2 year and 4 year A1cs and, although not significant, trended towards a correlation at the 3 year visit. Those with the poorest control at the 1-year interval nearly uniformly remained in very poor control at the 4 year interval, with a mean A1c at the 4 year mark of 9.7%, whereas 55% of patients in the good control group achieved an A1c of ≤ 8 at 4 years.

Although A1c at 1 year does not allow a practitioner to predict the trajectory of glycemic control over the subsequent 3 years, the mean group differences in the poorest and best control groups at 1 year suggest that identifying and targeting children with type 1 DM with poor glycemic control one year after diagnosis may be a way of allocating educational resources to those at greatest risk. This is important since, even with close follow up by a comprehensive diabetes team, only 26% of children achieved the target glycemic control for age at the 4-year follow up visit, demonstrating the difficulties in achieving adequate glycemic control. Anecdotally, practitioners have noted that children with higher A1cs early in their diabetes treatment have poor glycemic control longitudinally. However, this study provides objective data to substantiate these observations. It is difficult to identify which of the myriad of factors contribute to higher A1cs at 1 year, but noting that these individuals will continue to have high A1c levels in the future is important clinically.

Interestingly, children who eventually went on insulin pumps by the 4-year follow up had a lower A1c at diagnosis. At our facility, placement on pump therapy is determined in part by the family's ability to maintain adequate glycemic control on injection therapy prior to pump start. The lower A1c at diagnosis in children eventually using pumps indicate that A1c at diagnosis has some predictive power for the subsequent course of diabetes, specifically in relation to parental compliance. However, there was not a specific A1c at diagnosis that discriminated future pump use, and none of the other clinical variables we examined at diagnosis correlated significantly with A1c at 4-year follow up.

Although we had good long-term follow-up rates, our results are limited by a few factors. First, the retrospective nature of the study did not allow for collection of all pertinent clinical variables and laboratory data at each interval. Missing and uncollected data may have changed our results, specifically regarding individuals who did not have an A1c at diagnosis and were excluded *a priori*. We are also a large tertiary care center, and referral bias may skew results towards more ill patients with higher A1c levels at diagnosis. Our diabetic population is followed by a team consisting of pediatric endocrinologists, nurse practitioners, dietitians, and social workers. Thus, the resources available to our patients may differ from those available at smaller centers and may affect outcomes at each follow up interval.

While A1c is an useful marker of current and perhaps future control, attention to other risk factors known to affect diabetes care adversely, such as residing in a single parent household [13] and poor compliance with appointments [14], may also help determine which children should be the recipients of intensified resources. In future, large-scale studies with increased rates of follow up are needed in order to determine how best to identify patients at risk for poor control in their disease course in order to design interventions to improve long-term outcomes.

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Fig. 1.

(A) Correlation of age at diagnosis (in years) with A1c at diagnosis demonstrating increasing A1c with increasing age. The best fit linear regression line between the variables is plotted ($r = 0.23$, $p = 0.019$). (B) Correlation of symptom duration and A1c at diagnosis demonstrating increasing A1c with more symptomatic days. The best fit linear regression line between the variables is plotted ($r = 0.219$, $p = 0.026$).

Table 1
Patient characteristics at diagnosis (N = 120, except when otherwise indicated).

Characteristics	Mean $\pm$ SD (range)
Age (years)	7.6 $\pm$ 3.9 (1–17)
Gender	67 F/53 M
Race	110 Caucasian 8 African American 1 Hispanic 1 not recorded
Duration of reported symptoms (days)	22 $\pm$ 22 (0–120)
BMI z-score <i>N</i> = 71	−0.40 $\pm$ 1.6 (−5.3 to +3.1)
Bicarbonate (mmol L ^{−1}) <i>N</i> = 109	19.2 $\pm$ 7.2 (6–32)
Type of insurance	Private insurance 69% Medicaid 26% self pay 5%
Discharge regimen	79 sliding scale 41 carbohydrate to insulin ratios

Table 2
Correlations of A1c at diagnosis and A1c at 1 year with A1c levels at all other intervals.

	A1c Diagnosis	A1c 1 year
A1c 6 week	$r = 0.35, p = 0.02$	$r = 0.08, p = 0.4$
A1c 1 year	$r = -0.10, p = 0.19$	
A1c 2 year	$r = 0.03, p = 0.744$	$r = 0.61, p < 0.01^*$
A1c 3 year	$r = 0.29, p < 0.01^*$	$r = 0.18, p = 0.05^*$
A1c 4 year	$r = 0.18, p = 0.07$	$r = 0.31, p < 0.01^*$

* Bolded text indicates statistical significance.