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Stature at Time of Diagnosis of Type 1 Diabetes Mellitus

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Abstract

Objective. To assess the stature of children with type 1 diabetes mellitus at diagnosis.

Methods. We collected data from 451 records of children who were examined in a pediatric diabetes clinic and used data from the Third National Health and Nutrition Examination Survey for 10 522 children as control group. Analytical techniques included linear and logistic regression modeling. A semiquantitative meta-analysis evaluated 38 earlier publications that contain information on height at the onset of diabetes.

Results. Children <1 year of age were shorter than their peers by 1 standard deviation, whereas those from 3 years to near puberty were taller by approximately 0.3 standard deviation. Adjusting for parental height caused this difference to disappear for the older children but not for the infants. The meta-analysis results paralleled these observations.

Conclusions. Taller children generally seem to experience increased risk for development of diabetes mellitus type 1, except perhaps during infancy or early adolescence. This observation may have implications regarding pathogenesis of this disorder.

Keywords

Height, meta-analysis, NHANES III, growth

Several reports examined the heights of children at initial diagnosis of type 1 diabetes mellitus (DM-1) previously but failed to achieve consensus regarding growth patterns.¹⁻⁹ Some suggested that, depending on age or gender, heights of children with diabetes exceeded those of their peers; others failed to demonstrate this phenomenon, and a few reported shorter stature. Confirmation of a height discrepancy might provide some insight into the pathogenesis of DM-1. Increased height could support either the hypothesis that excess insulin secretion during the prodromal phase induces increased growth or that taller children experience increased risk of the development of DM-1. Increased growth tends to be associated with altered cellular regulatory functions.

Before the onset of symptoms, children with DM-1 exhibit islet cell hyperplasia accompanied by a period of increased insulin secretion.¹⁰ Similarly, the nondiabetic, identical twin siblings of patients with DM-1 demonstrate increased serum concentrations of basal insulin and C-peptide.^{11,12} If insulin promotes linear growth, then children who are passing through this prodromal phase of anabolism and hyperinsulinemia may experience enhanced growth velocity, leading to increased height at diagnosis.

We explored this relationship in 2 ways. An analysis was conducted of a large cohort of children examined by 1 of us, as well as a semiquantitative meta-analysis of all identifiable, previously published reports of the growth status of children at the time of diagnosis. The cohort study differs from earlier reports in several ways. It was larger and contained a higher proportion of infants and toddlers, increasing its power to detect height differences. For comparison, we used a large, scientifically selected, contemporaneous population, which increased validity and power. Finally, the availability of parental height reports allowed us to control for this important determinant of childhood stature in our analyses. This enhanced our ability to assess the direction of causality in the relationship between

height and disease state and perhaps determine whether diabetes induced taller stature or taller stature led to an increased risk of diabetes.

METHODS

We reviewed the records of 451 children who ranged in age from 1 month to 18 years and whose DM-1 was diagnosed between 1988 and 1998 in the Pediatric Diabetes Clinic at the Medical College of Wisconsin. The recorded time of initiation of insulin therapy represented the date of onset. We excluded records that were missing growth measurements within 3 months of diagnosis, those with type 2 diabetes, and those that had previously diagnosed medical conditions or environmental circumstances that potentially affected growth (eg, celiac or thyroid disease, chromosomal aberrations, methylphenidate therapy, history of any chronic disease, foster care). After these exclusions, 446 records—representing 217 girls and 229 boys—remained for analysis. The endocrine clinic nurse, specially trained in the technique, measured all children using the same stadiometer (Holtain Limited, Crymych, Wales, United Kingdom). Their parents provided heights by recall—a method of previously demonstrated validity.^{13,14}

Children who participated in the Third National Health and Nutrition Examination Survey (NHANES III) composed the control group.¹⁵ From 1988 through 1994, NHANES III examined 13 944 children between 2 months and 18 years of age, including detailed anthropometric measurements, parental heights, and family history. They oversampled the 2-month to 6-year age groups. We excluded children with medical conditions as noted above, as well as those whose parents reported any of these conditions before 18 years, or diabetes at any time. After also excluding those who were missing height or parental height measurements, 10 522 remained as a comparison population. We assigned *z* scores in standard deviations (SD) to all children based on this group.

Statistical Analysis and Data Sources

We compared the mean *z* score of the entire cohort of children with diabetes with that of the control group using the Student *t* test. All other analyses used regression techniques. Despite the relatively large cohort size, statistical power considerations mandated some data grouping to perform satisfactory age analysis. Therefore, with the exception of the 1-year-old and 2-year-old data points, each analysis used a variation of the moving average technique.¹⁶ For example, the calculations for the data point representing age 4 used ages 3, 4, and 5 data. This approach carried forward through the age 17 data point but leads obviously to the omission of ages 3 and 18 data points. The age 1 data point represents all children younger than 365 days, whereas the age 2 data point represents all children between 1 and 2 years. We chose to assess the 1- and 2-year age groups separately because preliminary data analysis suggested an inflection in the height–diabetes association in this range.

The relationships among height (*z* score), age, gender, diabetic status, maternal height, and paternal height were modeled using linear and logistic regression with the “regress” and “logistic” commands, respectively, in the statistical software package Stata, (version 5; Stata Corporation, College Station, TX). The linear regression model used *z* score as the dependent variable with age, sex, diabetic status, maternal height, and paternal height as covariates, whereas in the logistic model, diabetic status and *z* score changed places. We also examined the relationship by age between height and diabetic status

for each sex separately using linear regression. The Stata *t* test command compared the mean *z* scores for the 2 groups.

Meta-analysis

Using standard Medline search techniques, we identified relevant publications, then traced every seemingly appropriate reference in these reports.¹⁷ This approach led to the identification of 46 earlier studies for potential analysis. Several had little useful information, or the initial reference misquoted or misinterpreted the results; after review and exclusions, 36 remained. Few articles included the information needed for a quantitative meta-analysis, so we could not combine the results for all children. We did, however, examine the design of each, determining in particular its power to identify a difference between the study population and either a control group or standard population height values using the statistical software package, nQuery Advisor (Release 3.0; Statistical Solution Ltd, Cork, Ireland). In the former instance, we estimated power for a 2-sample Student *t* test, in the latter a 1-sample test. To achieve a power of 90% with a type 1 error rate of 5% and an intergroup difference of 0.25 SD requires 338 or 171, respectively, in each group. We chose the 0.25-SD interval based on our own data and information from earlier reports.

RESULTS

The entire diabetic group was taller than its NHANES III counterpart by approximately 0.2 SD ($P < .0001$); among the children who were older than 1 year, the difference was 0.22 SD ($P < .00005$). Infants with diabetes (<1 year) were shorter than their peers by approximately 1.0 SD, with the effect limited to boys—with a *z* score of -1.6 SD ($P < .002$; Fig 1, Table 1). During the second year, this difference disappeared. Subsequently, from time periods 4 (3–5 years) through 7 (6–8 years), children with diabetes exceeded their peers, with a maximum differential of 0.3 SD for period 4. During the pre- and early adolescent era, periods 8 (7–9 years) through 10 (9–11 years), heights were similar, but from period 11 through 14, the children with diabetes were again taller than their peers with a peak differential of 0.34 SD at period 12 (11–13 years). After 14 years, the differences in height again became insignificant. Girls with diabetes were taller until completion of the adolescent growth spurt, whereas boys exhibited a triphasic curve, initially shorter, then taller until age 8, then equal for several years, then taller again.

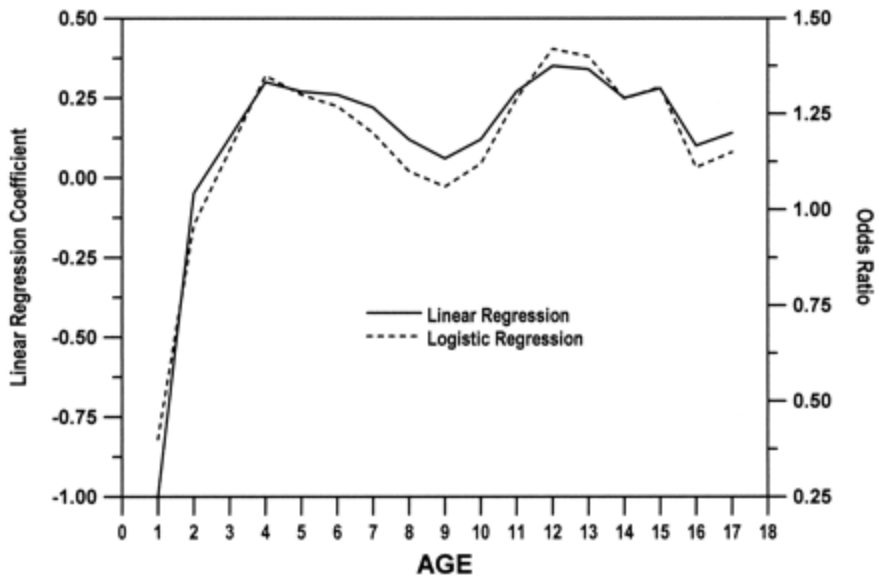


Fig 1. Linear and logistic regression results of modeling the relationship DM-1 and height at the onset by age. The linear regression coefficients represent the (unadjusted) difference in height between children with diabetes and NHANES III children; the odds ratio represents the risk of developing DM-1 associated with each SD increase in height.

TABLE 1. Moving Average Linear Regression Coefficients by Age

Age	All	P	Female	P	Male	P
1	-1.0	.009	0.15	.82	-1.63	.002
2	-0.05	.8	0.26	.42	-0.2	.4
3	NA	NA	NA	NA	NA	NA
"4"*	0.3	.004	0.34	.023	0.27	.075
"5"	0.27	.009	0.44	.006	0.15	.26
"6"	0.26	.01	0.3	.056	0.23	.08
"7"	0.22	.05	0.33	.061	0.15	.31
"8"	0.12	.32	0.16	.33	0.08	.65
"9"	0.065	.57	0.21	.15	-0.13	.46
"10"	0.12	.25	0.18	.19	0.04	.79
"11"	0.27	.008	0.29	.029	0.25	.123
"12"	0.35	.001	0.19	.22	0.5	.001
"13"	0.34	.004	0.27	.095	0.41	.017
"14"	0.25	.05	0.16	.39	0.33	.063
"15"	0.28	.07	0.3	.17	0.25	.24
"16"	0.1	.6	-0.01	.98	0.17	.5
"17"	0.14	.61	-0.07	.91	0.2	.54

NA indicates not applicable.

For all children adjusted for sex, and by sex. The coefficients represent the difference in height (in z score units) between children with diabetes and the control group.

* The unquoted numbers are actual ages; quoted numbers are midpoints of 3-year eras.

As expected, logistic regression models demonstrated a parallel but converse relationship between the risk for diabetes and height (Fig 1). During infancy, shorter children experienced a greater risk, but

subsequently the burden fell on taller children. Adjustment for parental stature eliminated any height differential in the linear regression model and risk differential in the logistic regression model, except during infancy, when the adjusted regression coefficients and odds ratios remained unchanged.

Meta-analysis

The 38 earlier reports and the present one fell naturally into 4 categories: 1) a sufficient number of participants to meet the power requirements determined above, accompanied by formal statistical analysis; 2) an insufficient number of participants, with some statistical analysis; 3) an insufficient number of participants, with a qualitative judgment of differences; and 4) identical twin studies (Table 2).^{1-9,18-46} Three investigations and the present one fit category 1; each found the children with diabetes generally taller, but a subset analysis in 1 found children <5 years shorter.⁹ In group 2, 11 studies found children with diabetes taller and 4 not significantly different. Ten of the 17 studies in group 3 found children with diabetes taller, 1 shorter, 4 the same height, and 2 either taller or the same depending on population standards. The study reporting shorter heights suggested a socioeconomic cause for the difference. The twin studies all came from the same institution, and at least some of the records seem to be identical, but the authors do not clarify this issue or reference their own earlier reports. The twins represented in the analysis compose fewer than half of the total followed—leading to the possibility of selection bias. Although the second twin to develop diabetes among the concordant pairs seemed to experience growth deceleration in the interval before the onset of clinical disease, the small sample size ($N = 16$) precludes statistically meaningful conclusions. Likewise, the absence of a comparison with population standards prevents making generalizable inferences.

TABLE 2. Publications Used in Meta-analysis

First Author	<i>N</i>	Power (%)	Results
Group 1			
Blom et al ¹⁸	337		Taller
Brown et al ⁹	184		0–5 shorter; 5–10 taller; 10+ same
Holl et al ¹⁹	436		Taller
Group 2			
Pond ²⁰	101		Boys/girls taller ($P < .05/.001$)
Evans et al ²¹	104	71	No difference
Drayer ²	62		Boys 4–9/4–14 taller; girls 4–9 shorter
Edelsten et al ³	44		Boys taller
Court et al ²²	121	77	No difference
Hjelt et al ²³	91		Taller ($P < .0125$)
Jefferson et al ²⁴	92		Taller (5–10)
Songer et al ⁴	200		0–4 shorter; 5–9 taller; 10–13 no difference; 14+ shorter
Emmerson and Savage ⁵	66	51	No difference
Price and Burden ⁶	115		Taller (up to 3 y before diagnosis)
Wise et al ⁸	122		Taller
Salerno et al ²⁵	62		Taller
Bognetti et al ²⁶	152		Taller

Scheffer-Marinus et al ²⁷	30		Taller ($P < .015$)
Choudhury and Stutchfield ²⁸	61	48	No difference
Group 3			
Joslin et al ²⁹	302		Taller
Priesel and Wagner ³⁰	38		Taller
Ladd ³¹	34		Taller
White ¹	100		Taller
Boyd and Nelson ³²	20		Taller
Spencer ³³	45		Taller
Rabinowitch and Bazin ³⁴	71		Taller
Fischer et al ³⁵	44		Taller
Jackson and Kelly ³⁶	120	77	No difference
Beal ³⁷	201	66	No difference
Hamne ³⁸	155		Shorter
Craig ³⁹	80	59	No difference
Jivani and Rayner ⁴⁰	116	76	No difference
Draminsky Petersen et al ⁴¹	99	69	No difference
Salardi et al ⁴²	79	59	No difference
Thon et al ⁷	89		Taller
DuCaju et al ⁴³	46		Taller
Group 4			
Tattersall and Pyke ⁴⁴	35		
Hoskins et al ⁴⁵	16		
David et al ⁴⁶	12		

Power analysis figures included for those studies reporting no difference in height between diabetic children and control group or standard population.

DISCUSSION

The results of our cohort analysis confirm and expand earlier suggestions that, at the time of diagnosis, the heights of children with DM-1 generally exceed those of their peers.^{19–21,27,33} The relatively small difference, 0.2 to 0.3 SD, may explain why some previous investigations failed to identify a discrepancy. These studies all had inadequate power to detect a difference of this size and provide virtually no evidence for the claim that the heights of children with diabetes at onset resemble those of their peers. The large number of children in each of our own groups led to high statistical support for the hypothesis that children with diabetes at diagnosis are taller than other children.

Efforts to control potential sources of bias during this investigation included measuring all children on the same stadiometer and maintaining a short interval between diagnosis and height determination—95% within 3 weeks. We considered 3 months as an acceptable upper limit because this time increment should have had little impact on any height differential present at the time of diagnosis. Data collection for NHANES III and our study was primarily contemporaneous. Four infants with diabetes were born after the completion of NHANES III, and some NHANES III adolescents came from slightly older birth cohorts than our oldest children. Bias attributable to secular trends should have

been most evident in these cohorts, 15 to 18 years, because those children had the largest potential discrepancy in birth years. In fact, the oldest children failed to exhibit differences in height and the infants with diabetes were shorter, making the issue of this potential bias effectively moot.

Among children between the ages of 3 and 8, as well as those between 10 and 15 years, measured heights exceeded those of the control group by approximately 0.3 SD. Analyses of the intervening ages, 8 through 10 years, perhaps failed to demonstrate discrepant heights because growth variability introduced by the timing of puberty overwhelmed any underlying relationship between diabetes and height.

In aggregate, earlier publications present a consistent picture of the stature of children with DM-1 at diagnosis. Their heights exceed those of their peers, except for the first few years, when some exhibited decreased stature, and the adolescent years, when no trends emerged. These results may seem somewhat surprising in view of the ongoing trend for publications to claim that earlier literature presents a confused picture—allowing for the inference of shorter, taller, or similar heights.^{5,9,18,26,43} We believe that our meta-analysis should definitively end such confusion, but with 2 caveats. First, some of the height differences in earlier reports might conceivably be attributable to secular trends. Publication bias—the alleged tendency for journals to publish only positive results—also must be considered. Clearly, the reports that we analyzed primarily found positive results, but for most—all but 4 papers—assessing the height at onset was a subsidiary finding, greatly reducing the likelihood of publication bias. We believe that neither potential source of bias substantially influences the preponderance of evidence from earlier reports. At diagnosis, children with diabetes from 5 to 10 years exceed their peers in height. Younger children—or perhaps only boys—may be shorter. Small average study size prevented adequate assessment of the relationship of sex to stature.

The observed differences between groups allow for reasoning about causality in 2 directions: diabetes mediates variations in growth, or growth variability influences risk for diabetes. Logically, statistical analyses support either interpretation: linear regression models view the impact of diabetes on height, whereas logistic models examine the impact of height on risk. Increased stature may represent an epiphenomenon of the islet-cell hyperplasia and hyperinsulinemia, which characterize the preclinical stages of diabetes.¹⁰⁻¹² The impact of parental height adjustment, however, biases us toward the hypothesis that increased stature enhances the risk of childhood diabetes, at least among the children older than 3 years. Children with diabetes were taller than their peers, but only by the amount attributable to their parents' increased stature. Unless we postulate that these children were initially shorter than expected, then grew taller as a consequence of presymptomatic diabetes, it is difficult to believe in the diabetes–growth causality direction. We therefore suggest that increased parental height leads to increased childhood height, which increases risk for diabetes. Accelerated intrauterine or childhood somatic growth, juxtaposed with a strong immunogenetic backdrop, may promote islet-cell destruction.^{47,48} Curiously, growth hormone therapy may increase the risk of DM-2 but not DM-1.⁴⁹

The short stature among our infants with diabetes suggests the possibility that small infants may experience increased risk for early-onset diabetes. Although recent evidence supports increased risk among larger or more rapidly growing infants for childhood-onset DM-1, these observations may represent some degree of differential pathogenesis between diabetes developing in infancy and diabetes developing later in childhood.^{47,48,50,51} Infants who are small at birth or during the first year of

life may experience intrauterine or early infantile stress, predisposing them to a variety of diseases in childhood and adulthood, including diabetes (type 2).^{52–54} Because parental height adjustment failed to modify the regression coefficient for height differential for infants, a perinatal environmental event seems most likely. Intrauterine growth retardation perhaps critically affects islet-cell development in some children. Alternatively, DM-1 may profoundly inhibit growth among younger boys before diagnosis—it would, however, require a reduction in growth velocity of 50% for approximately 3 months for the observed 1.6 SD decrement to develop. The meta-analysis provides additional support for these observations. Three reports found reduced heights in the 0 to 4 interval, 1 emphasizing boys.^{9,25,36}

CONCLUSION

The heights of children with newly diagnosed diabetes beyond infancy exceed those of age-matched control subjects (except pre- and early adolescent ages 8–10), seeming to reflect taller parental stature. This observation, as well as the diminished growth in infancy, may shed light on underlying pathogenic mechanisms and lead to new research directions regarding the cause of DM-1.

Footnotes

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- G.M. and K.M. are currently at the University of Alabama at Birmingham.

DM-1, type 1 diabetes mellitus • NHANES III, Third National Health and Nutrition Examination Survey • SD, standard deviation

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