



Growth in Children with HLA-Conferred Susceptibility to Type 1 Diabetes

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The incidence of type 1 diabetes (T1D) is increasing throughout the world. This trend may be explained by the accelerator hypothesis. Our study investigated growth, its biochemical markers, and their associations with the development of diabetes-associated autoantibodies (DAAB) in 219 children with genetic risk for T1D. Subjects were divided into risk groups based on their human leukocyte antigen genotype. Children in the moderate- to high-risk group were significantly taller when corrected to mid-parental height and had a lower insulin-like growth factor 1 (IGF-1)/IGF-1 binding protein (IGFBP-3) molar ratio than those in the low-risk group (corrected height standard deviation score 0.22 ± 0.93 vs. -0.04 ± 0.84 , $P < 0.05$; molar ratio 0.199 ± 0.035 vs. 0.211 ± 0.039 , $P < 0.05$). Children with DAAB tended to be taller and to have a higher body mass index than those with no DAAB. Our results suggest that the accelerator hypothesis explaining the increasing incidence of T1D may not solely be dependent on environmental factors, but could be partially genetically determined.

Keywords: HLA antigens; Diabetes mellitus, type 1; Body height; Body weight; Body mass index

INTRODUCTION

The incidence of type 1 diabetes (T1D) is increasing throughout the world. As the proportion of patients with human leukocyte antigen (HLA)-conferred risk for T1D has remained stable or decreased over time [1], environmental factors may be driving this trend.

A possible explanation for the increase in T1D incidence is the accelerator hypothesis, which states that due to overfeeding, obesity, and accelerated growth in early childhood, insulin production in beta-cells increases dramatically, and as beta-cells become overactive, they are more prone to autoimmune attack and destruction thereafter [2,3]. However, this hypothesis has mostly been tested retrospectively in children with diabetes-as-

sociated autoantibodies (DAAB) or T1D. Increased birth weight, accelerated height, and body mass index (BMI) gain in childhood have all been associated with development of DAAB and T1D [4-6]. Prospective studies in children with a genetic risk for T1D who have not yet developed DAAB or T1D are necessary to determine whether the accelerator hypothesis is purely dependent on background environment or works in combination with genetic factors. We have previously shown that children with the highest genetic risk gained less weight and length during the first 24 months of life than a control group [7].

Insulin-like growth factor 1 (IGF-1) and its binding protein (IGFBP-3), which are two main biochemical markers of growth in mid-childhood, a period when the incidence of T1D peaks [8], have been shown to be involved in the regulation of beta-

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cell growth and metabolism [9,10]. Changes in growth hormone and IGF-1 may lead to impaired linear growth and development of DAAB [11].

The aims of this study were to describe growth and its biochemical markers in children with HLA-conferred risk for T1D and to study the associations between growth parameters and the development of DAAB.

METHODS

From the Estonian DIABIMMUNE birth cohort [11], 219 children (110 boys) with HLA-conferred risk for T1D, but with no T1D diagnosis, were studied at the mean age of 8.8 years (range, 7.5 to 10.4) in 2017 to 2018. According to their HLA genotypes, the subjects were divided into high ($n=20$), moderate ($n=91$), and low genetic risk groups ($n=108$) [11,12]. For the statistical analysis, high- and moderate-risk subjects were combined as they shared a DQ8 allele, which confers the highest risk for T1D.

Growth

Height and BMI standard deviation scores (SDS) were calculated using World Health Organization reference data. Children with a BMI SDS above +1 and above +2 SDS were considered overweight or obese, respectively. Height SDS was corrected for mid-parental height (MPH). Growth data at 18 months from the DIABIMMUNE study were available in 202 children. Changes in height and BMI SDS (Δ) were calculated as the SDS at the study visit minus the SDS at 18 months. BMI results were compared with data of Estonian schoolchildren (aged 7.0 to 8.9 years) [13]. The majority of subjects were prepubertal ($n=213$); only six girls and four boys had reached Tanner stage 2.

Blood tests

Serum IGF-1 and IGFBP-3 levels were measured using the chemiluminescence method. The IGF-1/IGFBP-3 molar ratio was calculated considering their molecular weights. Four DAABs were measured in all subjects as described previously [11].

Statistical analysis

The Student's *t* test, Mann-Whitney *U* test, chi-square test, Fisher exact test, and a linear regression model were used for the analysis, which was conducted with R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

The Research Ethics Committee of the University of Tartu approved this study (IRB approval number 270/T-10 and 332/

M-15), which was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from a parent or guardian, and all children gave age-appropriate assent.

RESULTS

Growth

The mean height SDS and BMI SDS were not significantly different between the HLA risk groups. However, children in the moderate to high-risk group had a significantly higher corrected height SDS (0.22 ± 0.93 vs. -0.04 ± 0.84 , $P < 0.05$) (Table 1). In the linear regression model after adjustment for weight and sex, a higher genetic risk level for T1D was still associated with higher corrected height SDS ($P = 0.013$). In our cohort, 31% of children were overweight (20.5%) or obese (10.5%), which significantly exceeded the overall proportion of 23.5% ($P < 0.05$) in Estonian schoolchildren [13]. The difference was more pronounced in boys (37.2% vs. 26.3%, $P < 0.05$) than in girls (24.8% vs. 20.6%, $P > 0.05$).

Serum IGF-1 and IGFBP-3 concentrations

The mean serum IGF-1 and IGFBP-3 concentrations were not significantly different between the risk groups. However, the mean IGF-1/IGFBP-3 molar ratio was significantly higher in the low-risk group than in the high-risk group (Table 1).

Diabetes-associated antibodies

Fourteen children had developed at least one DAAB. Although the mean height and corrected height in the DAAB+ group were 0.37 and 0.26 SDS (equal to approximately 2 cm) higher than in the DAAB- group, the difference was not significant (Table 2). In addition, when the DAAB- group was divided into high and low genetic risk, significantly similar trends ($P = 0.04$) were seen in corrected height SDS and the IGF-1/IGFBP-3 molar ratio among the three groups; however, after Bonferroni correction, they were not significant (data not shown).

DISCUSSION

Our results suggest that the accelerator hypothesis is not purely dependent on environmental factors, but is also determined by genetic factors such as the HLA genotype. Prospective studies investigating growth in children with a genetic risk for T1D are limited. Our own results showed that during the second year of life, children with the highest genetic risk for T1D grew less in height and weight [7]. The Environmental Determinants of Dia-

Table 1. Growth Data and Biomarkers of Study Subjects According to Their Genetic Risk

Variable	Low risk (n=108)	Moderate to high risk (n=111)	P value
Age, yr	8.9±0.4	8.8±0.3	0.05
Height SDS	0.67±0.82	0.75±0.92	0.52
Corrected height SDS	-0.04±0.84	0.22±0.93	0.03
Weight SDS	0.62 (0.16 to 1.24)	0.71 (0.08 to 1.5)	0.59
BMI SDS	0.31 (-0.28 to 1.17)	0.36 (-0.42 to 1.2)	0.95
Overweight, %	21.3	19.8	0.87
Obese, %	8.3	12.6	0.38
IGF-1, µg/L	157.2±43.7	153.7±40	0.54
IGFBP-3, µg/mL	4.09±0.81	4.26±0.77	0.12
IGF-1/IGFBP-3 molar ratio	0.211±0.039	0.199±0.035	0.03
Δ Height SDS	0.16±0.85 (n=101)	0.18±0.85 (n=101)	0.85
Δ BMI SDS	-0.29 (-0.98 to 0.60) (n=101)	-0.22 (-1.17 to 0.62) (n=101)	0.83

Values are expressed as mean±1 standard deviation or median (interquartile range).

SDS, standard deviation score; BMI, body mass index; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; Δ, change between the present age and 18 months of age.

Table 2. Growth Data and Biomarkers of Study Subjects by Their DAAB Status

Variable	DAAB+ (n=14)	DAAB- (n=205)	P value
Age, yr	8.7±0.2	8.8±0.4	0.05
Height SDS	1.06±0.84	0.69±1.28	0.31
Corrected height SDS	0.31±1.18	0.07±0.87	0.47
BMI SDS	0.65 (-0.29 to 1.27)	0.3 (-0.36 to 1.16)	0.83
Weight SDS	0.87 (0.21 to 1.13)	0.66 (0.1 to 1.43)	0.58
Overweight, %	28.6	20	0.49
Obese, %	14.3	10.2	0.65
IGF-1, µg/L	139.4±38.5	156.5±41.9	0.13
IGFBP-3, µg/mL	3.94±0.86	4.2±0.79	0.29
IGF-1/IGFBP-3 molar ratio	0.195±0.028	0.206±0.038	0.19
Δ Height SDS	0.23±0.99 (n=13)	0.17±0.84 (n=189)	0.81
Δ BMI SDS	-0.48 (-1.44 to 0.36) (n=13)	-0.22 (-1.06 to 0.62) (n=189)	0.48

Values are expressed as mean±1 standard deviation (SD) or median (interquartile range).

DAAB, diabetes-associated antibodies; SDS, standard deviation score; BMI, body mass index; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; Δ, change between the present age and 18 months of age.

betes in the Young (TEDDY) study showed that the change in BMI from age 2 to 4 was not significantly different between HLA risk groups [14]. Our subjects were older than those in the TEDDY study [14], and since the main determinant of growth is dependent on child's age, this may explain the different findings. The variations in height depending on the HLA genotype could be explained by the impact of obesity causing faster linear growth and the role of IGF-1 and insulin resistance pathways in rapid weight gain [15]. However, since our children with higher genetic risk were not heavier than the low-risk group, these causes are unlikely to explain the differences.

We found that IGF-1/IGFBP-3 ratio, a marker of bioactive IGF-1, was significantly lower in children in the higher genetic risk group, which suggests that those children might have higher IGF-I sensitivity and need less bioactive IGF-1 to achieve good growth. IGF-1 and insulin are characterized by structural homology, have similar tyrosine kinase receptors, and share intracellular metabolic pathways [16]. Children with the lowest insu-

lin sensitivity also exhibited lower IGF-1 sensitivity, indicating that reduced sensitivity to insulin and IGF-I may coexist [16]. A positive association between stronger HLA-conferred susceptibility to T1D and better insulin sensitivity was seen in adults without diabetes [17]. However, as we did not collect data on insulin sensitivity, we cannot confirm this possibility.

We found that 31% of our subjects were overweight or obese, which significantly exceeded the overall proportion reported in 7- to 9-year-old Estonian schoolchildren studied in 2015 to 2016 [13]. This makes the secular trend of increasing obesity an unlikely reason. Our results are different from the TEDDY study, where children with increased genetic risk for T1D were leaner than the general population [14]. However, increased height and weight gain in childhood have been found to be associated with the development of islet autoimmunity or T1D, supporting the accelerator hypothesis [2,18,19]. Children who developed diabetes before 6 years of age were significantly taller from 6 to 18 months of age when corrected for MPH [3]. Al-

though not statistically significant, in our study the mean height SDS and corrected height SDS were both higher in the DAAB+ group, in which the prevalence of overweight or obesity was also particularly high (42.9%) compared to the general population [13] or those with no DAAB (30.2%). The Trial to Reduce Insulin-Dependent Diabetes Mellitus in Genetically at Risk (TRIGR) study showed that being overweight at 2 to 10 years of life was associated with a two-fold increased risk for the development of T1D [20].

Based on our findings, we cannot confirm that the accelerator hypothesis is solely dependent on environmental factors; instead, it more likely involves a combination of genetic and environmental factors. This proposal is supported by the fact that higher genetic risk itself was associated with increased corrected height, as well as the finding that the DAAB+ children tended to be taller and have a higher BMI than their DAAB- peers.

Our study has some limitations. Firstly, we did not have access to height and weight data between the age of 3 and 7–10. Secondly, the number of DAAB+ subjects in our cohort was small; therefore, the comparisons might not have had sufficient power to detect statistical significance.

In conclusion, we found that children with higher genetic risk for T1D were taller compared to their target height and had lower serum IGF/IGFBP-3 molar ratios than those with low risk. The prevalence of overweight or obesity in the entire cohort was significantly higher than in the general population. Further studies are needed to clarify whether these changes play a role in the development of diabetes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: L.S., A.P., V.T. Acquisition, analysis, or interpretation of data: L.S. Drafting the work or revising: L.S., A.P., V.T. Final approval of the manuscript: L.S., A.P., V.T.

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