Araştırma Makalesi *Research Article*

Pamukkale Tıp Dergisi
Pamukkale Medical Journal

doi:https://dx.doi.org/10.31362/patd.1058848

Evaluation of growth and effect of metabolic control on growth velocity in children with type 1 diabetes mellitus

Tip 1 diyabetes mellituslu çocuklarda büyümenin değerlendirilmesi ve metabolik kontrolün büyüme hızına etkisi

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Gönderilme tarihi:23.01.2022 Kabul tarihi:08.07.2022

Abstract

Purpose: One of the complications of diabetes mellitus is the disruption of growth. Evaluation of growth in type1 diabetes mellitus and the effect of metabolic control on growth velocity is aimed in this study.

Materials and methods: One hundred cases with Type1 diabetes mellitus are included and annual growth velocity, the status of metabolic control, and stage of puberties of cases are evaluated.

Results: There was no significant difference in height SDSs between at the time of diagnosis and current. Forty-three percent of the children had lower height than the genetic height potential. Evaluation of the relationship between Growthvelocity SDS and HbA1c values according to years showed a negative correlation in the third year. Evaluation of 23 cases that had attained final height presented no significant difference between height SDS at the time of diagnosis and final height SDS. Seventy-seven and a half percent of 18 cases satisfied the target height; 22.2% of cases attained a shorter final height than the target height based on evaluation with the reference to genetics. There was no difference between the metabolic controls.

Conclusions: Final height and growth velocity didn't appear to be affected in cases with good and intermediate metabolic controls; final height and growth velocity are negatively affected in cases with poor metabolic controls.

Key words: Type 1 diabetes mellitus in children, growth velocity, final height.

Gurcan Kaya N, Onder A, Cetinkaya S, Aycan Z. Evaluation of growth and effect of metabolic control on growth velocity in children with type 1 diabetes mellitus. Pam Med J 2022;15:772-778.

Öz

Amaç: Tip 1 diyabetes mellitus hastalığının komplikasyonlarından biri de büyümenin bozulmasıdır. Bu çalışmada tip 1 diabetes mellitusta büyümenin değerlendirilmesi ve metabolik kontrolün büyüme hızına etkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve yöntem: Tip 1 diyabetli 100 olgu çalışmaya dahil edildi ve olguların yıllık büyüme hızları, metabolik kontrol durumları ve puberte evreleri değerlendirildi.

Bulgular: Tanı anındaki boy SDS ile son boy SDS arasında anlamlı fark yoktu. Çocukların yüzde 43'ünün boyu genetik boy potansiyelinden daha düşüktü. Büyüme Hızı SDS ile HbA1c değerleri arasındaki ilişkinin yıllara göre değerlendirilmesinde üçüncü yılda negatif korelasyon görüldü. Final boya ulaşan 23 hastanın değerlendirilmesinde; tanıdaki boy SDS ile finaldeki boy SDS arasında anlamlı farklılık yoktu. Genetiğe göre değerlendirildiğinde ise %78 hastanın hedef boyu ile uyumlu, %22 hastanın hedef boyunun altında final boya ulaştığı görüldü. Metabolik kontroller arasında fark yoktu.

Sonuç: Bu çalışmada iyi ve orta metabolik kontrollü olgularda büyüme hızı ve final boyların etkilenmediği, kötü metabolik kontrollü olgularda ise olumsuz yönde etkilendiği sonucuna varıldı.

Anahtar kelimeler: Çocuklarda tip 1 diabetes mellitus, büyüme hızı, final boy.

Gürcan Kaya N, Önder A, Çetinkaya S, Aycan Z. Tip 1 diyabetes mellituslu çocuklarda büyümenin değerlendirilmesi ve metabolik kontrolün büyüme hızına etkisi. Pam Tıp Derg 2022;15:772-778.

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Introduction

Growth is a process that varies depending on nutrition, general health status, and psychological factors. Growth in chronic diseases such as Type 1 diabetes mellitus (DM) may be affected by the characteristics of the disease and its follow-ups [1]. In Type 1 DM, the relationship between the degree of metabolic control and growth was evaluated in various studies [2, 3]. Poor glycemic control is one of the most important factors affecting the growth in Type 1 DM [4]. Insulin plays an important role in regulation of the GH/IGFs axis. Expression of GH receptors is regulated by insulin in the liver and modulating post- GH receptor events affects the synthesis of IGFs and IGFBPs. Type 1 DM results in low portal insulin, GH hypersecretion, low circulating IGF-I and IGFBP-3, and high circulating IGFBP-1 [5].

In additiion, the effect of Type 1 DM on final height is also discussed in studies; however, studies evaluating the growth velocity (GV) and the relationship, between GV and metabolic control are limited [6, 7]. In this study, evaluation the growth of children with type 1 DM and the effect of metabolic control on GV was aimed.

Material and method

100 cases who were diagnosed with Type 1 DM in the Department of Endocrinology and followed up between 01.01.2005 to 31.12.2012 are included in the study. Children who had less than 1-year follow-up, reached the final height at the time of diagnosis, and had additional diseases (Coeliac, Autoimmune Thyroiditis) were excluded from the study.

Clinical informations of patients were scanned from electronic database. Age, gender, anthropometric evaluations, puberty stages, follow-up durations (diabetes age), insulin regimes, carbohydrate counting, complication statuses (presence of nephropathy, neuropathy, retinopathy), mean HbA1c levels of last one year, three and/or six-month GV, bone age (evaluated by a pediatric endocrinologist about Greulich-Pyle atlas) of cases were recorded. Anthropometric calculations (height and weight) of cases were calculated according to Turkish standards [8, 9].

The target height (TH) of patients were calculated according to their height of parents and the predictive final heights of cases were calculated according to the recent bone ages. Therefore, compliance between the recent heights and genetic THs in cases who had not attained final height was calculated by using the following formula;

Corrected height standard deviation according to genetic potential= Height SDS-TH SDS (Height SDS: recent measured height SDS). Children were subdivided into two groups according to their corrected height: children with corrected height ≥0 z-score are classified as suitable height; and those with corrected height <0 z score are classified as short stature [10]. In patients who reached the final height, it was determined whether their height could reach their TH.

Target and predicted adult height were calculated with formulas below:

Tarhet height (Girls) = (Mother height + Father height -13)/2

Tarhet height (Boys) = (Mother height + Father height +13)/2

Predicted adult height = Height / Coefficient based on bone age

The cases were divided into groups according to their insulin treatment regimens and mean HbA1c values.

Grouping according to the mean HbA1c: Good Metabolic Control; HbA1c<7.5%; Intermediate Metabolic Control; HbA1c: 7.5-9%; Poor Metabolic Control; HbA1c>9% [11].

The GV was calculated by finding the height difference between 1 year.

Statistical evaluation: SPSS for Windows version 15.0 is used for statistical analysis. Kolmogorov Smirnov test is used to evaluate the normality. Numerical variables were expressed as mean ± SD. Qualitative variables are expressed as numbers and percentages. Evaluation of difference between groups in respect of numerical variables is performed with a t-test if parametric test assumptions were checked. Evaluation of the difference in median values between groups in respect of qualitative variables is performed with the Kruskal-Wallis test. The relationship between numerical variables is examined with Pearson or Spearman correlation coefficients. Statistical significance is assigned as $p<0.05$.

Results

Fifty-one percent of 100 cases were girls. The mean age at the time of diagnosis and recent time was 8.4±3.4 and 12.0±3.8 years respectively. The mean follow-up time for type 1 diabetes was 3.7±1.7 years. The 30% of patients were at puberty tanner stage 1. No significant difference was found between the time of diagnosis and recent height SDS when evaluated by gender and puberty. However, the recent BMI SDS of all cases were significantly higher than the time of diagnosis. (Table 1)

Percentage of metabolic control status of cases in the first year; 58%, 38% and 4%; in the second year; 28.8%, 63.3% and 7.7; in the third year; 42.8%, 42.8% and 14.2; in the forth year; 33.3%, 56.4% and 10.3% for; in the fifth year; 35.4%, 41.9% and 22.5%; in the sixth year; 44.4%, 27.8% and 27.8% and in the seventh year; 30%, 40% and 30% for good, intermediate and poor metabolic control; respectively.

Five-year assessment of the correlation between annual mean HbA1c and GV SDS; it was seen that there was a negative correlation in the third year (R=-0.37, *p*=0.001), but there was no correlation in the other years (Table 2).

When metabolic control status and GV SDSs were compared, there was no significant difference in terms of GV SDS in the first and second year follow-ups. However; GV SDSs of cases with poor metabolic control are statistically lower than cases with intermediate and good metabolic control in the third year. The number of cases with poor metabolic control in the third year was significantly lower (Table 3). A statistically significant correlation is not observed between metabolic control and GV SDS, except for the third year.

The mean PH and mean TH of 52 patients whose PH and TH could be calculated were 170.1±9.6 cm, and 166.3±7.5 cm respectively. The mean of PH was statistically significantly higher than the mean of TH ($p<0.001$).

When the genetic compatibility of the 65 subjects (34 girls, 31 boys) who did not reach the final height was evaluated; it was observed that 37 (57%) of them were compatible with the genetic height potential, and 28 (43%) were below the genetic height potential. Of the 34 female subjects whose target height could be calculated and who did not reach the final height, 14 (41%) were genetically short, and 20 (59%) were genetically compatible. Of the 31 male cases whose target height could be calculated, 14 (45%) were genetically short, and 17 (55%) were genetically compatible. When evaluated according to genetics, it was seen that the final height of 78% of the study group

Table 1. Anthropometric characteristics of cases

AntropometricMeas	Anthropometric Measurements at the Time of Diagnosis	Current Anthropometric Measurements	*p*-value
Age (years)	8.49±3.42	12.08±3.80	-
Height SDS	0.04±1.19	0.02±1.06	0.876
Height SDS (Girl)	0.08±1.20	0.05±1.05	0.665
Height SDS (Boy)	-0.08±1.18	-0.01±1.09	0.528
BMI SDS	-0.60±1.32	-0.01±1.07	<0.001
BMI SDS (Girl)	-0.56±1.30	0.12±1.07	<0.001
BMI SDS (Boy)	-0.64±1.34	-0.15±1.06	0.003
Height SDS (prepubertal)	0.08±1.13	0.01±1.2	0.674
Height SDS (pubertal)	-0.04±1.23	-0.51±1.11	0.776

Table 2. Correlation of HbA1c and GV SDS by years

Year	Mean HbA1c	GV SDS	*p*-value
Year 1 (n:100)	7.4±1.0	0.30±1.85	0.13
Year 2 (n:90)	7.6±1.1	-0.08±2.04	0.74
Year 3 (n:70)	7.6±1.4	-0.56±2.40	0.001
Year 4 (n:40)	7.7±1.3	-0.37±1.90	0.41
Year 5 (n:32)	8.0±1.9	-0.24±2.51	0.86

Table 3. Relationship between metabolic control and GV SDS

Year	Good Metabolic Control		Intermediate Metabolic Control		Poor Metabolic Control		*p*-value
	% of cases	GV SDS	% of cases	GV SDS	% of cases	GV SDS	
Year 1	58	-0.07	38	0.62	4	0.72	0.60
Year 2	26	-0.11	57	0.01	7	0.53	0.63
Year 3	30	-0.42	30	-0.11	10	-2.32	0.04

was compatible with the TH; 22% of the patient had a lower final height, compared to the TH.

In the evaluation of 23 patients who attained the final height; the mean age of the cases at the time of diagnosis was 12.2±1.5 (9-15) years, the mean diabetes age was 4.6±1.4 (3-7) years, and the mean age at final height was 16.8±1.4 years. Height SDS at diagnosis was -0.35±1.20 SD, final height SDS was -0.38±1.24 and no significant difference was detected. There was no significant difference between final height SDS and SDS at the time of diagnosis in 12 girls. However, when 9 cases whose target height could be calculated were evaluated, it was observed that three of them (metabolic control status of these cases one good, one medium, one poor) attained the final height below the TH, and the others were at the final height suitable or longer than the TH. There was no significant difference between final height SDS and SDS at the time of diagnosis in 11 boys, who can be categorized under that subsection; however final height of 1 of 9 cases whose TH can be measured (the case had poor metabolic control) had shorter than TH.

Discussion

In this study, it was shown that there was no significant difference between the height SDS at the time of diagnosis and the current height SDS of Type 1 cases. The BMI SDSs were low at the time of diagnosis but increased after treatment. It was concluded that as HbA1c increased in the third year of the disease, there was a decrease in the growth velocity SDS, and the height SDS of those in the poor metabolic control group were lower compared to the third year metabolic control level. In addition, it was shown that there was no significant difference between the height SDS at the time of diagnosis and the final height SDS of the patients who reached the final height. It was determined that 78% of the children with type 1 diabetes reached a final height that was compatible with their genetic potential and 22% of them reached a shorter final height than their genetic potential, but this was not associated with metabolic control status.

Galera Martinez R. et al. [12], in their study with 52 patients, found that the height SDS at the time of diagnosis was 0.563 in boys and 0.734 in girls. After the follow-up, they found more significant growth reduction in prepubertal males and reported that boys had a slightly lower final height than the general population, and girls were similar to the general population. In the study of Timoteo et al. [13] were compared height at the time of diagnosis and final heights of 31 patients with Type 1 DM. They determined the height of the patients at the time of diagnosis slightly higher than the population. They showed the final heights within the normal limits according to both population and THs of the patients. Holl et al. [14], studied 436 children with Type 1 DM and they found significant growth failure in children who have been diagnosed in the pre-pubertal age period, compared to cases who have been diagnosed in the pubertal age group. In our study, when the height SDSs at the time of diagnosis and the final height SDS of the patients who reached the final height were compared, no statistically significant difference was found. Similarly, there was no significant difference between height SDS at diagnosis and current time in pubertal and prepubertal groups.

Despite the developments in diabetes treatment, glycemic control may not be at the desired level due to different reasons in children with Type 1 DM today. Studies show that only one third of children have HbA1c values below 7.5%, which is targeted by ISPAD [15]. In the study conducted by Çakır et al. [16]; in our country, they found that 24.5% of 200 patients with Type 1 DM had good metabolic

control, 41% had intermediate and 34.5% had poor metabolic control. In our study, when we compared the mean HbA1c levels of our cases with the literature, we found that the majority of them had good and moderate metabolic control. We attribute the glycemic control in our study to be better than the literature, because of being an old center with high experience in diabetes and providing good diabetes education. Although the number of cases in the good and moderate metabolic control group was sufficient in our study group, we think that the low number of cases with poor metabolic control may be misleading in the evaluation, and in this respect, such studies with a higher number of cases are needed.

Although nutritional, psychological and genetic factors are emphasized as the cause of growth retardation in children with diabetes, many researchers think that growth is also related to the degree of metabolic control [3]. On the other hand, some researchers emphasize that growth retardation is related to the duration of the disease rather than diabetes control [2]. It has been reported that growth retardation in diabetic children is especially related to the duration of the disease prepubertal period and is due to a delay and decrease in peak GV at puberty [17]. Donaghue et al. [18] grouped and compared 451 cases with Type 1 DM diagnosed between 1974-1990 and 1990-1995. They reported that cases with Type 1 DM grew better with modern treatment. As a result of increasing knowledge about both modern therapy and diabetes education, our cases had more “good metabolic control” compared to the past. The fact that the height SDS values of our cases did not change at diagnosis and at the last follow-up may also be related to their good metabolic controls.

Salerno et al. [19] evaluated 62 cases with normal height percentiles at the time of diagnosis. Similar to our study; they commented that puberty progressed normally, height percentiles were normal and these were independent of diabetes age, glycemic control and insulin therapy. Huang et al. [20] evaluated linear growth and metabolic control in their study. They found that pubertal girls were taller than the control group at diagnosis, and that prepubertal girls and boys were similar to the control group. They also suggest that cases have lost their height advantages in the following years; however, final heights are within normal limits and correlate with their heights at the diagnosis. The mean HbA1c value of patients was 10.3% and they did not find a correlation between final height or decreasing height with metabolic control or disease age [21].

The study is conducted in our country, Demir et al. [21] were observed a 5-year follow-up of 101 Type 1 DM patients and height SDSs annually. There was no significant change in mean height SDS. They found a negative correlation between GV and HbA1c in the third year of the disease. In our study, there was no significant difference between height SDSs at the time of diagnosis and follow-up in girls and boys with Type 1 DM. Different from the literature, in our evaluation of the relationship between annual GV SDS and HbA1c levels, no relationship was found between HbA1c and GV SDS, except for the third year of the disease. When the patients were grouped according to their metabolic control levels and compared with GV SDS, a relationship was found between HbA1c and GV SDS in the third year of the disease. In the third year, the GV SDSs of the patients with poor metabolic control was found to be more negative than those with good and moderate metabolic control. This means that our cases, which generally have good-moderate metabolic control and whose height SDS and GV SDS did not change, did not grow well in the third year when their metabolic control deteriorated, but we thought that this temporary situation did not affect the final height with the improvement of metabolic control in the following years. However, in our study, we observed that metabolic control deteriorated as the duration of diabetes increased.

As in other chronic diseases, the effect of growth in Type 1 DM is a controversial issue. Thus, PH should be estimated to have an idea about the height processes of cases. Scheffer Marinus et al. [22] compared PH and TH. They did not observe a correlation between PH and TH in 35 Type 1 DM patients. There are no similar studies in our country. In our study, PH is significantly higher than TH. PH and TH of both pubertal and pre-pubertal patients were estimated separately to observe the effects of age and puberty on PH. PH values of pre-pubertal and pubertal patients were higher and that relationship was significant in the pre-pubertal group. We conceive that PHs

might have been over-calculated just because our cases are at a tender age. In healthy individuals, the calculated PH becomes more significant with advancing age. We thought that the younger age of our cases caused the high calculation of PHs.

In our study, we calculated the TH SDS and genetically corrected height SDS of the cases in order to evaluate the genetic compatibility of the heights of Type 1 DM cases who did not reach the final height. When the genetic compatibility of the 65 subjects who did not reach the final height was evaluated; we found that 57% of them were compatible with the genetic height potential, and 43% were below the genetic height potential. In our cases, we continue to monitor their final heights for the convenience of these calculations. Although some formulas can be used to estimate the final height, the true score can be seen only when children reach their final height, because the process of growth is affected by various factors. Thus, we saw that 78% of our patients who reached the final height achieved the TH.

In conclusion; final height and growth velocity didn't appear to be affected in cases with good and intermediate metabolic controls; final height and growth velocity are negatively affected in cases with poor metabolic controls.

Conflict of interest: No conflict of interest was declared by the authors.

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This study represented as a poster in 'Ulusal Pediatrik Endokrinoloji ve Diyabet Kongresi' 2013-Edirne.

Ethics committee approval: This article is based on post-graduate/doctoral studies using research data before 2020.

Authors' contributions

Z.A. has constructed the main idea and hypothesis of the study. N.G.K., S.Ç., and A.Ö. have developed the theory and arranged/edited the material and method section. Z.A. and N.G.K. had evaluated the data in the Results section. Discussion section of the article written by N.G.K., Z.A., and S.Ç. reviewed, corrected, and approved. In addition, all authors discussed the entire study and approved the final version. It should be written after the sources.