Automatic Bone Age Determination in Adult Height Prediction for Girls with Early Variants Puberty and Precocious Puberty

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What is already known on this topic?

Predicted adult height (PAH), which is traditionally measured by the clinician using Bayley-Pinneau (BP) or Roche-Wainer-Thissen methods on the basis of bone age, is one of the parameters used in treatment decision-making in girls presenting with signs of precocious puberty.

What this study adds?

PAH-standard deviation score (SDS) calculations made with the BP method based on the Greulich-Pyle measurement of the BoneXpert program estimates the near-final height-SDS with the closest accuracy.

Abstract

Objective: In cases of precocious puberty, the determination of bone age (BA) is usually performed by clinicians using the Greulich-Pyle (GP) atlas, and there can be significant variation between assessors. The aim of this study was to compare predicted adult height (PAH) calculations based on BA read by the automated BA method "BoneXpert" (BX) with clinician-determined BA-based PAH calculations.

Methods: Girls who presented with suspicion of precocious puberty and normal pubertal variants, such as premature thelarche and premature adrenarche, and whose BA determined by both BX and two different clinicians were followed up until reaching near-final height (NFH). Those whose breast development started before the age of 8 years were considered as precocious puberty. Four PAH calculations were performed with two different estimated height calculation methods, the Bayley-Pinneau (BP) and Roche-Wainer-Thissen based on two different BA predictions (Clinician-GP and BX-GP). PAH-standard deviation score (PAH-SDS) and NFH-SDS values of the patients were compared.

Results: The median chronological age of the 44 girls included at presentation was 9.3 years, while the median BA was 10.4 years and 10.6 years according to clinician-GP and BX-GP, respectively; mean height-SDS was 0.75 and target height-SDS was -0.28. When they reached NFH, the height-SDS was -0.02. Final analyzes were performed in 26 cases who did not have low birth weight and did not receive puberty-arresting treatment. Delta PAH-SDS-NFH-SDS (Δ-SDS) was compared according to the four different PAH calculations. The closest PAH-SDS value measurement to NFH-SDS was calculated by BP based on BA determined by the BX-GP method (-0.09).

Conclusion: PAH calculations using the BP method based on BX-derived GP readings most accurately predict NFH in girls with precocious puberty, and normal pubertal variants.

Keywords: Bone age, BoneXpert, early puberty, normal puberty variants, predicted adult height

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Introduction

Early variant puberty is a source of concern for families and often leads to pediatric outpatient clinic visits. This concern primarily arises from the potential psychosocial challenges and fears that the child may have a shorter adult height (1,2). However, only 10% of children presenting with complaints of early variant puberty fulfills the criteria for precocious puberty (3). Some of the visits are due to premature thelarche and premature adrenarche, which are considered as normal variants of puberty. Premature thelarche is the onset of isolated breast development before the age of 8 years and is benign and self-limiting (4). Premature adrenarche is the onset of pubic or axillary hair growth in girls before the age of 8 years and there are no other accompanying pubertal findings. However, both situations may progress to precocious puberty and require follow-up (5).

Especially in the last 20 years, there has been an increase in cases of so-called "precocious puberty" in girls aged 7-9 years (1). Although the reason for this increase is not known, it is thought that various environmental, genetic, and hormonal factors may play a role in the etiology (6,7). One of the parameters that determine treatment and follow-up decisions in the management of these cases are evaluation of bone age (BA). Comparison of predicted adult height (PAH) based on BA with target height (TH) is one of the important criteria in deciding whether to start treatment or not (8,9).

BA determination can be performed by pediatric endocrinologists and radiologists using conventional BA atlases or by automated BA determination methods. Traditional methods are often used in Türkiye, but they have various limitations. The most important of these are that they are time-consuming, have high intra-rater and inter-rater variability, and make chronological comparison difficult (10).

Automated BA determination methods, on the other hand, provide instant results, eliminate assessor variability, and require only access to software. There are a number of ongoing studies in this field and the results are promising. The reliability of these programs has been verified by comparison with traditional methods (7).

The aim of this study was to compare the BAs measured by the BoneXpert (BX) method, one of the available automatic BA determination methods, with BA values traditionally determined by the clinician according to BA atlases. To evaluate which measurement method is the most successful in predicting near-final height (NFH) by comparing the PAH and PAH-standard deviation scores (SDSs) calculated based on these measured BAs with NFH and NFH-SDS in order to determine which method would be most appropriate to use when making treatment decisions in clinical practice.

Methods

Between June 2016 and November 2018, girls between the ages of 6 and 10 years who were admitted to the Pediatric Endocrinology Outpatient Clinic of Koç University Hospital with suspicion of precocious puberty were evaluated. Girls who were evaluated for BA by both the clinicians and the BX program during the first visit and continued to be followed up were included in the study. Those with chronic diseases, drug use that may affect weight gain or growth rate (such as steroids, psychostimulants, antiepileptics, thyroid hormone and growth hormone replacement therapy) were excluded from the study.

The ages, height, height-SDS, body mass index (BMI), BMI-SDS and pubertal stages of these cases were recorded at the time of first visit. Cases with breast development between stages 2 and 5 or pubic hair development between stages 2 and 5 with puberty onset after the age of 9 years were considered to have normal pubertal development. Those with puberty onset before the age of 8 years or between the ages of 8 and 9, breast development in stages 2-5 or pubic hair growth in stages 2-5 and luteinizing hormone (LH) level < 5 IU/L were considered as early variant puberty. Cases with breast development between stages 2-5, no pubic hair and peak LH level < 5 IU/L were considered as premature thelarche. Cases with pubic hair in the range of stage 2-5, no breast development and peak LH level < 5 IU/L were considered as premature adrenarche. Cases with a peak LH level ≥5 IU/L or LH/follicle stimulating hormone ratio > 0.66 or LH ≥0.3 IU/L with onset of breast development before the age of 8 years were considered as true central precocious puberty (CPP) (11).

At the time of initial presentation, BA determination was performed by two pediatric endocrinologists using the Greulich-Pyle (GP) atlas (clinician-GP), and by the BX method according to the GP (BX-GP) in two different ways. In the evaluations performed by clinicians, the BA value was decided by taking the arithmetic mean of the BA value determined by two different clinicians (12). The BA calculation with BX takes place in three different stages. In the first stage, it reconstructs and validates 15 bones, including the radius, ulna, all metacarpals, and all phalanges of fingers 1, 3 and 5. It rejects bones that are not correctly positioned or are severely dysmorphic. In the second stage, the BA value is determined for each bone separately. If a BA value deviates from the mean of all bones by more than 2.4

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years, it is not evaluated. If less than 8 bones are valued, an average BA value is not reported. In the third stage, it converts the average of these values according to the GP and Tanner-Whitehouse (TW) scale (13).

Then, four different PAHs were calculated using two different estimated height calculation methods; Bayley-Pinneau (BP) and Roche-Wainer-Thissen (RWT). These different PAH values were: PAH_1 - the PAH calculated by BP based on the BA determined by the clinician using the GP method; PAH_2 - the PAH calculated by RWT based on BA determined by clinician using GP method; PAH_3 - the PAH calculated by BP based on BA determined by BX-GP method; and PAH_4 - the PAH calculated by RWT based on BA determined by BX-GP method. The BP method calculates PAH using tables based on the principle that each BA represents a percentage of the child's adult height. The RWT method uses sex- and age-specific coefficients to calculate the PAH based on the child's recumbent length, weight, BA and the mid-parental height (MPH) (12).

The attainment of final height (FH) or NFH of these cases were assessed by looking at the annual growth rate and BA. An annual growth rate of less than 1cm or a BA of 14 or more was considered as NFH (14). To determine BA, left hand-wrist radiography was taken and evaluated with the BX program. To ensure a more uniform study group, participants with a history of low birth weight and those who received puberty-arresting treatment at the baseline or during follow-up were excluded from the final analysis. The final evaluation was conducted with 26 cases (Figure 1). Four different PAH and PAH-SDS values, NFH and NFH-SDS, TH and TH-SDS, and PAH-SDS - NFH-SDS difference (Δ-SDS) of these cases were compared. In addition, correlations between the calculated PAHs, as well as their relationships with MPH were analyzed.
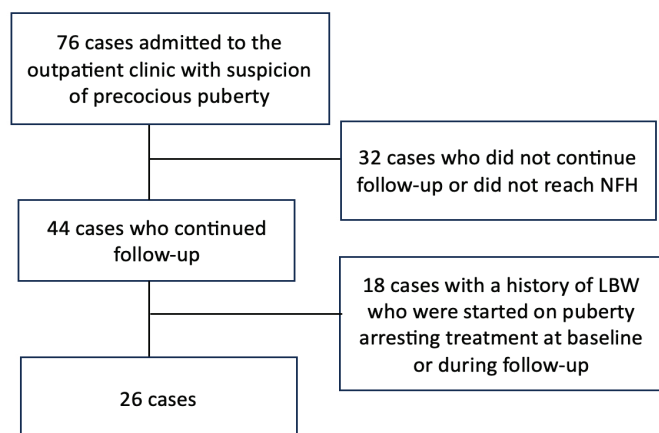
Figure 1. Consort diagram

LBW: low birth weight, NFH: near final height

The Olcay Neyzi growth charts were used to calculate the auxological data through www.ceddcozum.com (15). PAH_{1-4} calculations were also made on the same website by using PAH calculator (15). The approval of the Koç University Faculty of Medicine Ethics Committee dated 19.01.2022 and protocol number 2022.006.IRB1.006 was obtained for this study, which was designed as a single-center, retrospective cohort study. Written informed consent was obtained from the parent/legal guardian of participants prior to the study.

Statistical Analysis

Data were analyzed in the Statistical Package for the Social Sciences, version 26 program (IBM Corp, Armonk, NY, USA). The median and interquartile range values were used to describe continuously distributed variables; frequency and percentage terms were used to describe categorical variables. Mann-Whitney U test in independent groups, Wilcoxon test in dependent groups and Friedman test in more than two dependent groups were used to determine statistically significant differences in pairwise group comparisons for continuous variables that were not normally distributed. Paired group comparisons were made with the Wilcoxon test to determine which of the groups the difference was between. Chi-square test was used to determine the statistical difference between categorical variables and Fisher's exact test was used if the expected value was below 5. Spearman's correlation analysis was used to evaluate the correlations of variables with each other. A value of $p < 0.05$ was considered statistically significant.

Results

Of the 44 cases who were followed up until reaching NFH, 25 (56.8%) were diagnosed as early variant puberty, 6 (13.6%) as CPP, 5 (11.4%) as premature thelarche, and 8 (18.2%) as premature adrenarche at presentation. The median chronological age (CA) and BA at presentation of these cases were 9.29 years and 9.97 years, respectively. Median height and height-SDS at the first visit were 137.8 cm and 0.71. Median BA was 11 years according to clinician-GP and 10.7 years according to BX-GP. At the last visit, the median NFH and NFH-SDS were 158.4 cm and -0.76, and the median TH and TH-SDS were 161.2 cm and -0.32.

The demographic characteristics of the study group (n = 26) in which the final analyzes were conducted are given in Table 1. Of these cases 11 (42.3%) were diagnosed as early variant puberty, 6 (23.1%) as CPP, 4 (15.4%) as premature thelarche and 5 (19.2%) as premature adrenarche. The median BA estimates of these cases were 10.4 years according to clinician-GP and 10.6 years according to BX-GP (p = 0.620). The interobserver coefficient of variation for the

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BA value was 0.966 (95% confidence interval 0.952-0.975). The median value of NFH and NFH-SDS were 158.4 cm and 0.02, respectively.

The PAH-SDSs of the cases according to their BAs calculated by clinician-GP and BX-GP and the comparisons of them with TH-SDS and NFH-SDS are shown in Table 2. There was a significant difference between PAH_1-SDS calculated with BP based on clinician-BA measurement and PAH_2-SDS calculated with RWT (p = 0.011), whereas there was no significant difference between PAH_3-SDS calculated by BP based on BX-GP measurement and PAH_4-SDS calculated

Table 2. Comparisons of the PAH-SDSs to TH-SDS and NFH-SDS

Median	Median	p
PAH_1-SDS (-0.4)	TH-SDS (-0.28)	0.684
PAH_1-SDS (-0.4)	NFH-SDS (0.02)	0.298
PAH_2-SDS (-0.2)	TH-SDS (-0.28)	0.021
PAH_2-SDS (-0.2)	NFH-SDS (0.02)	0.611
PAH_3-SDS (-0.25)	TH-SDS (-0.28)	0.849
PAH_3-SDS (-0.25)	NFH-SDS (0.02)	0.409
PAH_4-SDS (-0.25)	TH-SDS (-0.28)	0.037
PAH_4-SDS (-0.25)	NFH-SDS (0.02)	0.696

PAH: predicted adult height, SDS: standard deviation score, TH: target height, NFH: near final height

by RWT (p = 0.137). When PAH-SDSs, NFH-SDS and TH-SDS were compared statistically, there was no significant differences between them (p = 0.080). In the correlation analysis between PAH-SDSs, the closest correlation was found between PAH_1-SDS and PAH_3-SDS (r = 0.758, p≤0.001). PAH_1-SDS was significantly lower than PAH_2-SDS (p = 0.011) and PAH_4-SDS (p = 0.019). PAH_1-SDS, PAH_2-SDS, PAH_3-SDS and PAH_4-SDS were statistically similar to NFH-SDS (p_1 = 0.298, p_2 = 0.611, p_3 = 0.409, p_4 = 0.696). PAH_1-SDS and PAH_3-SDS were statistically similar to TH-SDS (p_1 = 0.684, p_2 = 0.849) while PAH_2-SDS and PAH_4-SDS were significantly greater than TH-SDS (p_3 = 0.021, p_4 = 0.037).

The differences (Δ-SDS) between PAH-SDS and NFH-SDS were analyzed. Specifically:

- The difference between PAH_1-SDS and NFH-SDS (Δ1-SDS) was -0.20.

- The difference between PAH_2-SDS and NFH-SDS (Δ2-SDS) was 0.18.

- The difference between PAH_3-SDS and NFH-SDS (Δ3-SDS) was -0.09.

- The difference between PAH_4-SDS and NFH-SDS (Δ4-SDS) was 0.18.

There was a significant difference between the Δ-SDS values. In pairwise comparisons, Δ1-SDS was significantly higher than Δ2-SDS (p = 0.011). However, the following pairs were statistically similar:

- Δ1-SDS and Δ3-SDS (p = 0.414)

- Δ1-SDS and Δ4-SDS (p = 0.190)

- Δ2-SDS and Δ3-SDS (p = 0.101)

- Δ2-SDS and Δ4-SDS (p = 0.750)

- Δ3-SDS and Δ4-SDS (p = 0.137)

Among the PAH-SDS calculations, PAH3-SDS (Δ3-SDS: -0.09) was the closest to NFH-SDS.

Table 1. At initial presentation, anthropometric datas, puberty stages, target heights, BA values according to clinician and BX program, and PAHs (n = 26)

	Median (IQR)
Age, years	9.3 (8.7-9.5)
Height, cm	136.4 (132-142.7)
Height-SDS	0.75 (0.2-1.5)
Height age	9.7 (8.9-10.6)
BMI, kg/m^2	18 (15.9-19.2)
BMI-SDS	0.7 (-0.2-1.1)
Thelarche, %	
1	8
2	38
3	31
4	23
5	-
Pubarche, %	
1	34
2	27
3	31
4	4
5	4
BA by clinician-GP, years	10.4 (8.9-11)
BA by BX-GP, years	10.6 (9.1-11.1)
PAH_1 (cm)	160.8 (155.6-164.4)
PAH_1-SDS	-0.4 (-1.2-0.23)
PAH_2 (cm)	161.8 (160-164.5)
PAH_2-SDS	-0.2 (-0.53-0.25)
PAH_3 (cm)	161.6 (157.7-164.8)
PAH_3-SDS	-0.25 (-0.93-0.29)
PAH_4 (cm)	161.6 (160.3-164.5)
PAH_4-SDS	-0.25 (-0.47-0.24)
TH, cm	161.3 (157.3-163)
TH-SDS	-0.28 [-0.98-(-0.01)]
NFH, cm	158.4 (154.8-161.7)
NFH-SDS	0.02 (-0.7-0.3)

BA: bone age, BMI: body mass index, BX: BoneXpert, GP: Greulich-Pyle, PAH: predicted adult height, IQR: interquartile range (25th-75th percentile), SDS: standard deviation score, TH: target height, NFH: near final height

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In the study group, age at presentation, height, height-SDS, BMI, BMI-SDS, HA, thelarche stage, pubarche stage, TH and menarche age were statistically similar when the cases who reached TH (n = 20) and those who did not reach TH (n = 6) were compared with each other. The median value of NFH was 159.8 cm and the median value of NFH-SDS -0.54 in those who achieved TH, while the median values of NFH was 152.4 cm and the median value of NFH-SDS was -1.68 in those who did not achieve TH and there was a significant difference between them (p_1 = 0.045, p_2 = 0.015).

Discussion

The results of this study showed that the BA-based PAH-SDS calculation determined by the BX-GP in girls with precocious puberty and normal pubertal variants was found to be closest to the NFH-SDS. In a study by van Rijn et al. (16) in which the BX program was used as an automatic BA determination method, it was observed that BA was measured 0.28 years behind in boys and 0.2 years behind in girls compared to CA in 226 healthy male and 179 female cases and it was concluded that the BX program was a reliable BA prediction tool. In a study in which 13 male and 103 female patients with a diagnosis of precocious puberty were evaluated, automatic BA measurements made by the clinician and BX were compared and it was found that the mean difference between BX-GP BA and clinician-GP-BA was -0.19 (17). In another study in which 392 patients were evaluated, it was found that BX-GP BA was not significantly different from clinician-GP BA, but BX-TW BA was significantly lower than clinician-BA (18). As in previous studies, the present study found the difference between BX-GP BA and Clinician-GP BA to be similar (median 0.005 years, p = 0.620)

BA assessment can be performed using different methods and based on these, PAH calculations can be made with different methods. In a study conducted by Jeong et al. (19) three different BA assessment methods used by pediatric endocrinologists were compared and it was shown that PAHs calculated by BP, TW2 mark, and RWT showed a good correlation with NFH and when the PAH-NFH difference was considered, PAH calculation by BP method was found to have a closer estimation compared to TW2 mark and RWT methods. In another study conducted by Akın Kağızmanlı et al. (12) the BAs of 48 girls who were treated for puberty precocity were evaluated to compare PAH estimations according to BP, RWT and TW2 methods. These authors reported that the closest estimate to NFH was that made using the BP method. Roemmich et al. (20) reported that the method with the closest PAH estimation was TW2, followed by RWT and BP, respectively. In the study by Brämswig et al. (21) it was reported that the best prediction method for

male cases was RWT, whereas the three methods were not different from each other for female cases. Some studies have shown that the RWT method, which also takes TH into account, leads to an overestimation of PAH (2). In the present study and similar to the studies by Jeong et al. (19) and Akın Kağızmanlı et al. (12), the closest PAH measurements to NFH were those based on BP method.

There are very few published studies evaluating FH/NFH based on BA and PAH calculations using the BX method. In a study of 82 patients, 48 of whom were female, with chronic endocrinopathy (congenital adrenal hyperplasia, growth hormone deficiency), BA determination was analyzed both conventionally (by clinician) and using the GP method with BX and PAH was calculated. The mean PAH calculated by the BX method was 156.2 cm and 153.9 cm by the conventional method and the mean NFH evaluated during the transition of these patients to the adult endocrinology outpatient clinic was 156.3 cm (13). In two different studies by Thodberg et al. (23), 231 healthy children in the first and 108 healthy children in the second were followed until they reached FH/NFH (22). In both studies, the mean squared error was used to evaluate the model performance and it was concluded that the BX method provides an objective PAH calculation. In the present study, the median NFH of the cases in the group in which the final analyses were performed was 158.4 cm and NFH-SDS was 0.02. In this group, TH was 161.4 cm and TH-SDS was -0.28 SDS. In the evaluation of PAH by four different methods in these cases, PAH-SDS calculations by Clinician-GP-BP method and PAH-SDS calculations by BX-GP-BP method were similar to each other, but the closest measurement to NFH-SDS was the measurement made by the BX-GP-BP method.

Study Limitations

This study is not without its limitations. It has a small sample size, as not all invited cases could participate in the study. The low participation rate may be related to the Coronavirus disease-2019 pandemic during the follow-up period of our research. Some of the subjects presented to the study with a single parent; therefore, height measurements of both parents could not be performed and therefore, the calculation of TH had to be based on verbal information obtained from the family. Another limitation of this study is that PAH calculations based on RWT were performed based on height measured while standing.

Conclusion

The BX automated BA determination method seems to have the closest estimation for NFH-SDS in cases of precoccious puberty and early pubertal variants. It may be preferable

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in terms of being a more objective option, ease of use and time-saving. The BA estimates obtained with this method, and the adult height estimates based on this, may make it possible to give parents who are already worried during outpatient visits a range rather than a single adult height estimate. However, further research on larger groups is needed before the widespread use of automated BA determination systems is common.

Ethics

Ethics Committee Approval: The approval of the Koç University Faculty of Medicine Ethics Committee dated 19.01.2022 and protocol number 2022.006.IRB1.006 was obtained for this study, which was designed as a single-center, retrospective cohort study.

Informed Consent: Written informed consent was obtained from the parent/legal guardian of participants prior to the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: All authors contributed equally to all contribution sections.

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