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Research Article

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

Yigit MH et al. Use of an Automated Bone Age Programme to Estimate Predicted Adult Height

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What is already known?
Predicted adult height, which is traditionally measured by the clinician using Bayley Pineau or RWT 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?
Predicted adult height-SDS calculations made with the BP method based on the GP measurement of the BoneXpert program estimates the Near final height-SDS with the closest accuracy.

Abstract
Introduction: 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 is to compare predicted adult height (PAH) calculations based on BA read by the automated bone age method (BoneXpert) with clinician-determined BA-based PAH calculations.
Method: A total of forty-four girls who presented with suspicion of precoccious puberty and normal pubertal variants such as premature thelarche and premature adrenarche, and whose BA determined by both BoneXpert 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 2 different estimated height calculation methods [Bayley Pineau-BP and Roche-Wainer-Thissen-RWT] based on two different BA predictions [Clinician-GP and BoneXpert-GP). PAH-standard deviation score (PAH-SDS) and NFH-SDS values of the patients were compared.
Results: The median chronological age at the presentation was 9.3 years, while the median BA was 10.4 years and 10.6 years according to Clinician-GP and BoneXpert-GP, respectively; mean height-SDS was 0.75 and TH-SDS was -0.28. When they reached NFH, the height-SDS was -0.02. Final analyzes were performed on 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 4 different PAH values. 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 BoneXpert-derived GP readings most accurately predict near-final height 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 has become a source of concern for families in recent years 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 and there are no other accompanying pubertal findings. However, both situations may progress to precocious puberty and requires 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 exactly, 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).
Bone age 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 Turkey, 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. A number of ongoing research in this field and the results are very 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 automatic BA determination methods, with the 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-SDSs calculated based on these measured BAs with NFH and NFH-SDS. By this way, it was aimed to determine which method would be more appropriate to be used in making treatment decisions in clinical practice.

Method

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. Forty-four girls who were evaluated for BA by both the clinicians and the BoneXpert (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-standard deviation score (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 or between the ages of 8 and 9, breast development in stages 2 - 5 or pubic hair growth in stages 2 - 5 and LH level <5IU/L were considered as early variant puberty. Cases with breast development between stages 2-5, no pubic hair and peak LH level <5IU/L were considered as premature thelarche. Cases with pubic hair in the range of stage 2 to 5, no breast development and peak LH level <5IU/L were considered as premature adrenarche. Cases with a peak LH level ≥ 5IU/L or LH/FSH ratio >0.66 or LH ≥ 0.3 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 BoneXpert 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 I, III and V. 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 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 TW scale (13).

Then, 4 different PAHs were calculated using 2 different estimated height calculation methods (Bayley Pineau [BP], and Roche-Wainer-Thissen [RWT]). (PAH_1: PAH calculated by BP based on the BA determined by the clinician using the GP method; PAH_2: PAH calculated by RWT based on BA determined by clinician using GP method; PAH_3: PAH calculated by BP based on BA determined by BX-GP method; PAH_4: 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 (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 BoneXpert 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. Additionally, correlations between the calculated PAHs, as well as their relationships with mid-parental height (MPH) were analyzed.

The Olcay Neyzi growth charts were used to calculate the auxological data through www.ceddcozum.com. PAH_{1-4} calculations were also made on the same website by using predicted adult height calculator (15). The approval of the Koç University School of Medicine Ethics Committee dated 19.1.2022 and protocol number 2022.006.IRB1.006 was obtained for this study, which was designed as a single-center, retrospective cohort study.

Statistical Analysis

Data were analyzed in SPSS 26 IBM program. The median and interquartile range (IQR)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 difference in pairwise group comparisons in 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 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 were diagnosed as early variant puberty, 6 as central precocious puberty, 5 as premature thelarche, and 8 as premature adrenarche at presentation. The median chronological age (CA) and HA 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, 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 of them were diagnosed as early variant puberty, 6 as CPP, 4 as premature thelarche and 5 as premature adrenarche. The median BA estimates of the cases were 10.4 years according to Clinician-GP, 10.6 years according to BX-GP and there was no statistically significant difference between them (p: 0.620). The interobserver coefficient of variation for the BA value was 0.966 (95% CI 0.952-0.975). The median value of NFH and NFH-SDS were 158.4cm 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 statistically significant difference between PAH_1-SDS calculated with BP based on clinician-BA measurement and PAH_2-SDS calculated with RWT, whereas there was no statistically significant difference between PAH_3-SDS calculated by BP based on BX-GP measurement and PAH_4-SDS calculated by RWT (p_1:0.011, p_2:0.137). When PAH-SDSs, NFH-SDS and TH-SDS were compared statistically, there was not a statistically significant difference 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 and PAH_4-SDS (p_1: 0.011, p_2: 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 statistically similar to TH-SDS while PAH_2-SDS and PAH_4-SDS significantly higher than TH-SDS (p_1:0.684, p_2:0.849, p_3:0.021, p_4:0.037).

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

- The difference between PAH1-SDS and NFH-SDS (Δ1-SDS) was -0.20.
- The difference between PAH2-SDS and NFH-SDS (Δ2-SDS) was 0.18.
- The difference between PAH3-SDS and NFH-SDS (Δ3-SDS) was -0.09.
- The difference between PAH4-SDS and NFH-SDS (Δ4-SDS) was 0.18.

There was a statistically significant difference among 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 ($p = 0.019$)
- 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.

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 caught TH (n:20) and those who did not catch 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 caught TH; the median values of NFH was 152.4 cm and the median value of NFH-SDS was -1.68 in those who did not catch TH and there was a statistically significant difference between them (p_1: 0.045, p_2: 0.015).

Discussion

The results of this study revealed that the BA-based PAH-SDS calculation determined by the BX program -GP method in girls with precocious puberty and normal pubertal variants was found to be closest to the NFH-SDS. In a study by Rijn et al. 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 reported that the BX program was a reliable BA prediction tool (16). 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). In our study, similar to other studies, the difference between BX-GP BA and Clinician-GP BA was statistically 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. 3 different BA assessment methods applied by pediatric endocrinologists were compared and it was shown that PAHs calculated by BP, TW2 Mark, RWT showed a high 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 (19). In another study conducted by Akın Kağızmanlı et al. the BAs of 48 girls who were treated for puberty precocity were evaluated to compare PAH estimations according to BP, RWT and TW2 methods. It was seen that the closest measurement to NFH was the measurement made by BP method (12). Roemmich et al. reported that the method with the closest PAH estimation was TW2, followed by RWT and BP, respectively (20). In the study by Bramswig et al. 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 (21). Some studies have shown that the RWT method, which also takes TH into account, leads to an overestimation of PAH (2). In our study, similar to the studies by Jeong et al. and Akın Kağızmanlı et al., the closest PAH measurements to NFH were those based on BP method (12, 19).

There are very few studies in the literature 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 (22). In two different studies by Thodberg et al. (23,24), 231 healthy children in the first and 108 healthy children in the second were followed until they reached FH/NFH. In both studies, the Mean Squared Error (MSE) was used to evaluate the model performance and it was concluded that the BX method provides an objective PAH calculation.

In our study, the median NFH of the cases in the group 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 4 different methods in these cases, PAH-SDS calculations by Clinician-GP-BP method and PAH-SDS calculations by BX-GP-BP method were statistically similar to each other, but the closest measurement to NFH-SDS was the measurement made by BX-GP-BP method.

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 Covid-19 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 measured 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 BoneXpert automated BA determination method seems to have the closest estimation for NFH-SDS in cases of precoccious puberty and early pubertal variants. It may preferable in terms of being a more objective option, ease of use and time savings. 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 case groups is needed in the future for the widespread use of automated BA determination systems.

Authorship Contributions:

M.H.Y, E.E, S.H, G.Y.M designed the study, M.H.Y and E.E, collected the data, M.H.Y and E.E performed data analysis, M.H.Y, E.E, S.H, and G.Y.M. wrote the manuscript. All authors approved the final version of manuscript.

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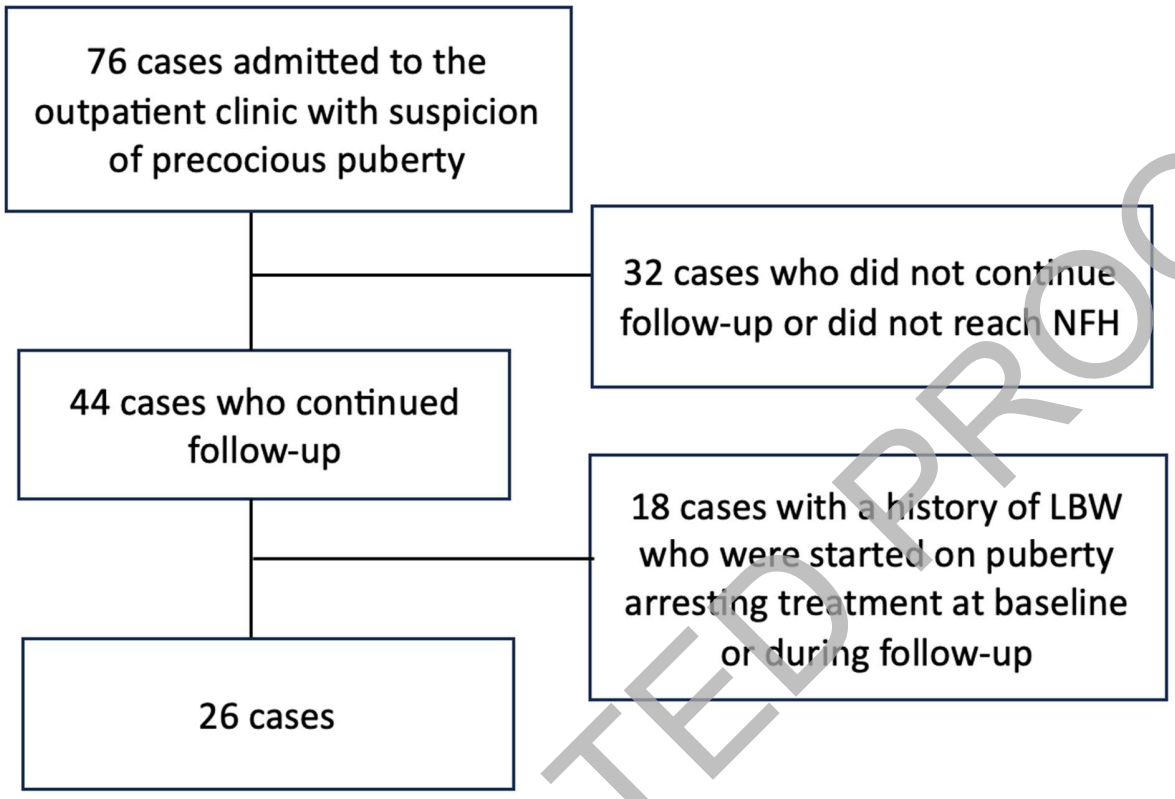
Figure 1. Consort diagram



*LBW: low birth weight; NFH: near final height

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 2 3 4 5	 8 38 31 23 -
Pubarche, % 1 2 3 4 5	 34 27 31 4 4
BA- Clinician-GP, years	10.4 (8.9 – 11)
BA- 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, IQR: Interquartile range (25^{th}-75^{th} percentile) SDS: standard deviation score, TH: target height

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

		p
PAH_1-SDS	TH-SDS	0.684
PAH_1-SDS	NFH-SDS	0.298
PAH_2-SDS	TH-SDS	0.021
PAH_2-SDS	NFH-SDS	0.611
PAH_3-SDS	TH-SDS	0.849
PAH_3-SDS	NFH-SDS	0.409
PAH_4-SDS	TH-SDS	0.037
PAH_4-SDS	NFH-SDS	0.696

* The median values of PAH_1-SDS: -0.4; PAH_2-SDS: -0.2; PAH_3-SDS: -0.25; PAH_4-SDS: -0.25; TH-SDS: -0.28; NFH-SDS: 0.02.