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ORIGINAL ARTICLE

Bone age determination in eutrophic, overweight and obese Brazilian children and adolescents: a comparison between computerized BoneXpert and Greulich-Pyle methods

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Abstract

Background Bone age determination is usually employed to evaluate growth disorders and their treatment. The Greulich-Pyle method is the simplest and most frequently used type of evaluation, but it presents huge interobserver variability. The BoneXpert is a computer-automated method developed to avoid significant bone age variability among distinct observers.

Objective To compare the BoneXpert and Greulich-Pyle methods of bone age determination in eutrophic children and adolescents, as well as in overweight and obese pediatric patients.

Materials and methods The sample comprised 515 participants, 253 boys (159 eutrophic, 53 overweight and 41 obese) and 262 girls (146 eutrophic, 76 overweight and 40 obese). Left hand and wrist radiographs were acquired for bone age determination using both methods.

Results There was a positive correlation between chronological age and Greulich-Pyle, chronological age and BoneXpert, and Greulich-Pyle and BoneXpert. There was a significant increase (P<0.05) in bone age in both the Greulich-Pyle and BoneXpert methods in obese boys when compared to eutrophic or overweight boys of the same age. In girls, there was an increase in bone age in both obese and overweight individuals when compared to eutrophic girls (P<0.05). The Greulich-Pyle bone age was advanced in comparison to that of BoneXpert in all groups, except in obese boys, in which bone age was similarly advanced in both methods.

Conclusion The BoneXpert computer-automated bone age determination method showed a significant positive correlation with chronological age and Greulich-Pyle. Furthermore, the impact of being overweight or obese on bone age could be identified by both methods.

Keywords Bone age · BoneXpert · Children · Greulich-Pyle · Hand · Obesity · Radiograph · Wrist

Introduction

Bone age determination is a measure of bone maturation, and it is usually employed to investigate growth disorders, to follow-up growth therapy and to predict adult height [1, 2]. Traditionally, bone age determination adopts the Greulich-Pyle method, which is a holistic technique described in 1959 by William Walter Greulich and Sarah Idell Pyle [3]. The Greulich-Pyle method is based on a comparison of hand and wrist radiographs with a standard atlas of radiographs compiled according to gender and age, varying from birth to 18 years old [2].

The Greulich-Pyle method's advantages include being a fast and low-cost technique, but with significant interobserver variability, perhaps associated with the presence of gaps

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between standardized ages, as well as quite subtle changes from year to year, eventually determining imprecision and divergent results [4, 5].

The BoneXpert is a computer-automated method developed by Thodberg [6], presenting as one of its characteristics the ability to reduce interobserver variability in bone age assessment [2, 7]. This method evaluates bone age according to bone shape, density and the degree of epiphyseal fusion [8]. BoneXpert has been validated for use in eutrophic North American, Caucasian, African-American, Hispanic and Asian children [8–10]. It has also been validated for use in congenital adrenal hyperplasia, juvenile idiopathic arthritis [11, 12] and central precocious puberty [13]. The technical limitations of this method are related to the requirement of a minimal image post-processing to allow proper analysis.

The present study includes eutrophic children and adolescents, and adds an important subset of pediatric patients who are overweight or obese, aiming both to compare the Greulich-Pyle and BoneXpert methods of bone age determination and to establish the usefulness of the automated method when evaluating overweight or obese patients.

Materials and methods

This is a prospective cross-sectional descriptive study, which included 515 individuals (305 eutrophic and 210 overweight or obese), 253 boys (159 eutrophic, 53 overweight and 41 with obesity) and 262 girls (146 eutrophic, 76 overweight and 40 with obesity).

Children and adolescents were recruited from four schools in São Paulo, Brazil, three public and one private, between October 2016 and June 2017. Obese patients attending the Pediatric Endocrinology Unit of Irmandade da Santa Casa de Misericórdia de São Paulo hospital were also included. Inclusion criteria comprised children and adolescents of both genders, ages 5 to 17 years old, who agreed to take part in the study with the authorization of their parents or guardians. The Institutional Ethics Committee approved the study and all participants agreed to participate in the study and their parents/guardians also gave written consent.

The exclusion criteria were previous chronic, endocrine or metabolic diseases (i.e. hepatopathy, diabetes mellitus, kidney disease, Cushing syndrome, hypo/hyperthyroidism); genetic syndromes, chronic use of medications (i.e. antihypertensive, lipid-lowering agents, hypoglycemic drugs, hormones and steroids) and conditions that do not allow precise height measurement (i.e. bone dysplasia or deformities, rickets and severe scoliosis). Twenty-eight of the 543 cases were excluded because of short stature and chronic and genetic disease (n=4), tall stature (n=15) and primary undernutrition (n=9).

The anthropometric evaluation included weight (Tanita InnerScan BC-533, Tokyo, Japan) and height measurements (AlturaExata anthropometer, Belo Horizonte, MG, Brazil), and calculation of body mass index (BMI) scored against the World Health Organization international reference [14]. BMI and height standard deviation (SD) score data used the same international reference [14]. Before bone age determination, participants were arranged by gender and BMI SD score in eutrophic (-1 to + 1SD), overweight (+1 to + 2SD) and obese groups (>+2SD).

During school visits, left hand and wrist radiographs were performed by a specialized technician, employing a mobile device (Portable X-Ray Poskom PXM20BT and CR Carestream Vita, Rochester, NY). The following parameters were used: Filter AL: 2 mm, distance: 100 cm (40 in), focal point: 1.25 mm, tube voltage: 45 kv and exposition: 1.6 mAs. Radiographs obtained in the outpatient clinic were acquired and stored using a PACS workstation. All images, including those obtained with the portable device were digital and stored as DICOM (Digital Imaging and Communications in Medicine) file extensions before the rating by the experts or the analyses by the BoneXpert software. The bone age determination employed the Greulich-Pyle method. Three experts – two pediatric endocrinologists (C.K., with 26 years of experience, and C.A.L., with 38 years of experience) and one radiologist (R.A., with 35 years of experience) – independently rated the images in a single time interval not exceeding 15 days. For Greulich-Pyle analyses, the only known participant clinical information was gender. The final bone age was established after agreement of at least two of the experts. Discordant bone ages were reanalyzed by the same experts during a consensus meeting to obtain a consensus bone age. To establish the bone age, no interpolation was used, defining the bone age by the most closely image pattern according to the Greulich-Pyle standards.

The same images were evaluated using the automated computer method (BoneXpert Standalone, v 2.5.0.1, 2013, Hørsholm, Denmark).

The statistical analysis was accomplished with SigmaStat for Windows version 3.5 (SPSS, Systat software, San Jose, CA). A paired t-test was applied to compare the single individual bone age evaluated using the Greulich-Pyle and computer-automated methods. An ANOVA (analysis of variance) test was applied to compare bone age in the three BMI groups (eutrophic, overweight and obese). The correlation between both methods (Greulich-Pyle and BoneXpert) was assessed using the Pearson correlation coefficient and the Bland-Altman analysis was used for their comparison. A P value <0.05 was considered statistically significant.

Results

There was no difference between the bone age data acquired from public or private schools, allowing collective presentation of the results. In this study, using the Greulich-Pyle method, identical bone age assessment was reported by the three experts in only 38% of the cases; in 62%, the same bone age was rated by at least two of the experts. We also calculated the amplitude of variability in bone age rating separated for girls and boys. Mean (SD) variability was 1.0 (0.9) years and 1.1 (0.6) years. The maximum variability among observers was 2.25 years and 2.5 years for girls and boys, respectively. Maximum variability in bone age rating was in around 10% of radiographs, essentially occurring when the second observer rated one standard below and the third observer rated one standard above the mean bone age rated by the first observer.

The anthropometrics and consensus bone age values are shown in Table 1. No significant difference was found between genders in the distinct groups. There was a positive correlation between chronological age and Greulich-Pyle; chronological age and BoneXpert, and Greulich-Pyle and BoneXpert (Table 2).

The differences between bone age and chronological age are shown in Fig. 1. When obese boys were compared to eutrophic or overweight boys, a bone age advancement was observed with both the Greulich-Pyle and BoneXpert methods ($P<0.05$). There was no significant difference in bone age between eutrophic and overweight boys regardless of the method used to determine bone age. In girls, there was bone age advancement in both obese and overweight girls when compared to eutrophic girls. However, this observation was present only with the Greulich-Pyle method. When the BoneXpert method was used, the bone age advancement was identified in obese girls when compared to eutrophic or overweight girls. The Greulich-Pyle method rated a more advanced bone age than the BoneXpert method in all groups, except in obese boys, in which advancement of bone age was similar in both methods. The Bland-Altman test was used to recognize the rate of concordance between the two methods (Fig. 2) in the three groups classified according to BMI. Both methods were highly concordant, but a major discordance was observed in peripubertal age. The extent of variation between BoneXpert and Greulich-Pyle was also determined by calculating the root-mean-square error (RMSE) (Table 2). RMSE values varied among BMI groups from 0.8 to 1.1 years.

Table 1 Anthropometric data and bone age (years) observed in boys and girls divided according to the body mass index

Boys	Eutrophic (*n*=159) mean (SD)	Overweight (*n*=53) mean (SD)	Obese (*n*=41) mean (SD)
Chronological age (years)	11.2 (3.2)	11.8 (3.3)	10.2 (2.4)
Height SD score	-0.04 (0.8)	0.09 (0.8)	1.1 (1.0) *
BMI SD score	-0.1 (0.7)	1.4 (0.3)	2.9 (0.6) #
Greulich-Pyle (years)	11.3 (3.9)	12.1 (3.9)	11.4 (3.2)
BoneXpert (years)	10.8 (4.0)	11.7 (4.3)	11.2 (3.1)
Greulich-Pyle – chronological age (years)	0.16 (1.3)	0.34 (1.3)	1.20 (1.7) *
BoneXpert – chronological age (years)	-0.42 (1.3)	-0.06 (1.6)	1.01 (1.6) *,&
Girls	Eutrophic (*n*=146) mean (SD)	Overweight (*n*=76) mean (SD)	Obese (*n*=40) mean (SD)
Chronological age (years)	11.2 (3.1)	10.9 (3.0)	10.1 (2.4)
Height SD score	0.02 (0.9)	0.29 (0.8)	0.92 (1.1) #
BMI SD score	-0.12 (0.8)	1.41 (0.3)	2.65 (0.5) #
Greulich-Pyle (years)	11.9 (3.5)	12.0 (3.6)	11.7 (3.4)
BoneXpert (years)	11.2 (3.7)	11.3 (3.8)	11.2 (3.3)
Greulich-Pyle – chronological age (years)	0.71 (1.1)	1.13 (1.1)	1.66 (1.5) #,&
BoneXpert – chronological age (years)	0.06 (1.2)	0.42 (1.2)	1.14 (1.3) *,&

Boys:

*obese vs. eutrophic; obese vs. overweight (ANOVA, $P<0.05$)

between all groups (ANOVA, $P<0.05$)

& Greulich-Pyle–chronological age vs. BoneXpert–chronological age in eutrophic and overweight (*t*-test, $P<0.05$)

Girls:

Height SD score, BMI SD score, Greulich-Pyle–chronological age between all groups (ANOVA, $P<0.05$)

*BoneXpert-chronological age in obese x eutrophic and obese x overweight (ANOVA, $P<0.05$)

& Greulich-Pyle–chronological age x BoneXpert–chronological age (*t*-test, $P<0.001$ in all groups)

ANOVA analysis of variance, *BMI* body mass index,

SD standard deviation

Table 2 Pearson's coefficient of correlation (R) and root-mean-square error (RMSE) between methods of bone age determination in individuals grouped according to the body mass index

	Chronological age vs. Greulich-Pyle	Chronological age vs. BoneXpert	Greulich-Pyle vs. BoneXpert
Boys			
Eutrophic	R=0.948	R=0.955	R=0.973/RMSE=1.09
Overweight	R=0.953	R=0.943	R=0.977/RMSE=1.03
Obese	R=0.847	R=0.858	R=0.967/RMSE=0.82
Girls			
Eutrophic	R=0.956	R=0.952	R=0.982/RMSE=0.96
Overweight	R=0.959	R=0.963	R=0.979/RMSE=1.06
Obese	R=0.923	R=0.943	R=0.980/RMSE=0.86

The coefficients of correlation were all significant at the level of $P<0.001$

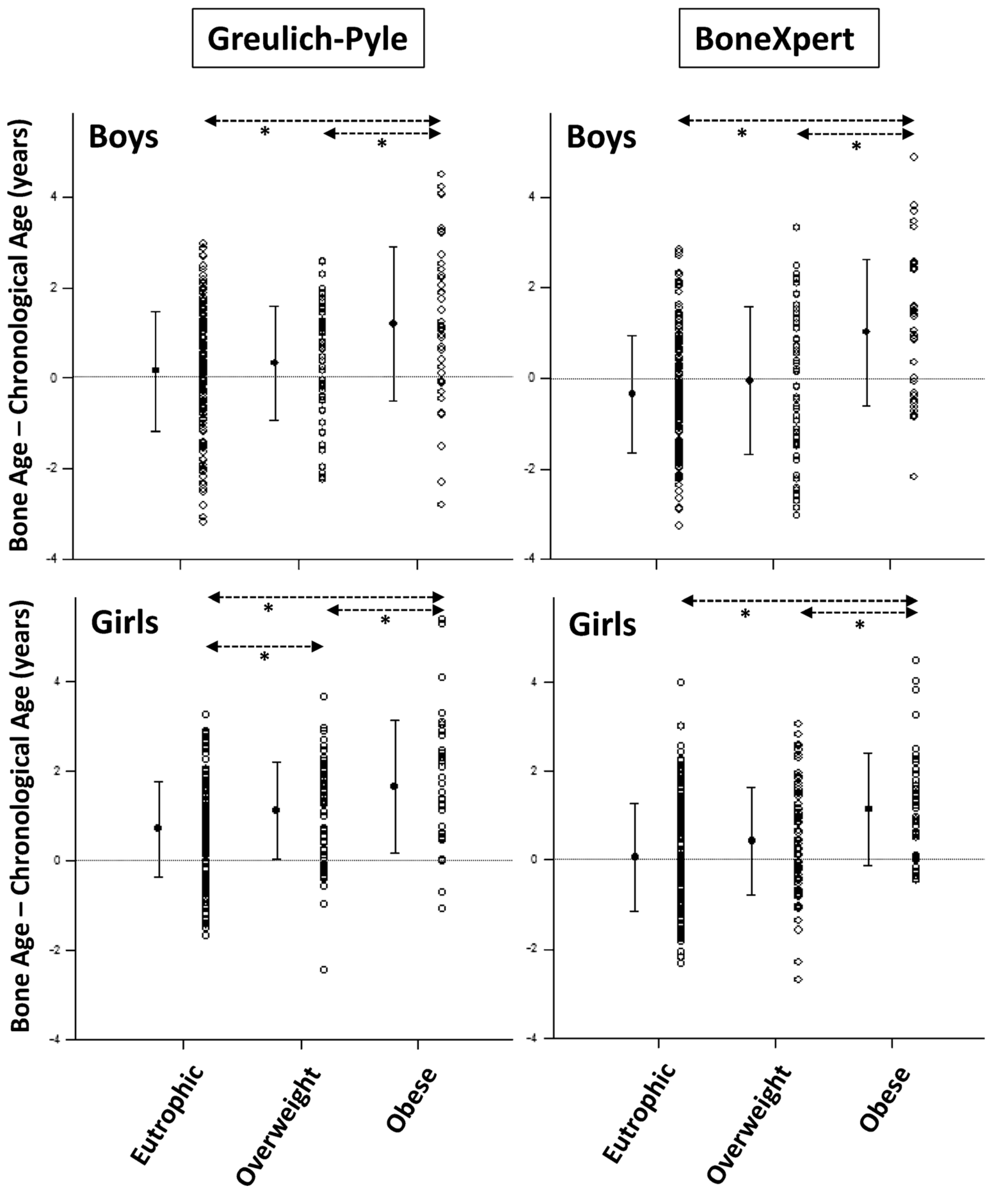

Fig. 1 Differences between bone age (determined by Greulich-Pyle and BoneXpert methods) and chronological age, according to gender and body mass index stratified as eutrophic, overweight or obese. *Vertical bars* indicate standard deviation, with the center dots indicating the mean. *Double-headed arrows* indicate comparison between the patient groups. Bone age was significantly advanced (*) in obese patients when determined using both Greulich-Pyle and BoneXpert methods. A more severe interference of obesity was observed when employing the Greulich-Pyle rating, especially in girls, in whom significant bone age advancement was observed even in overweight girls

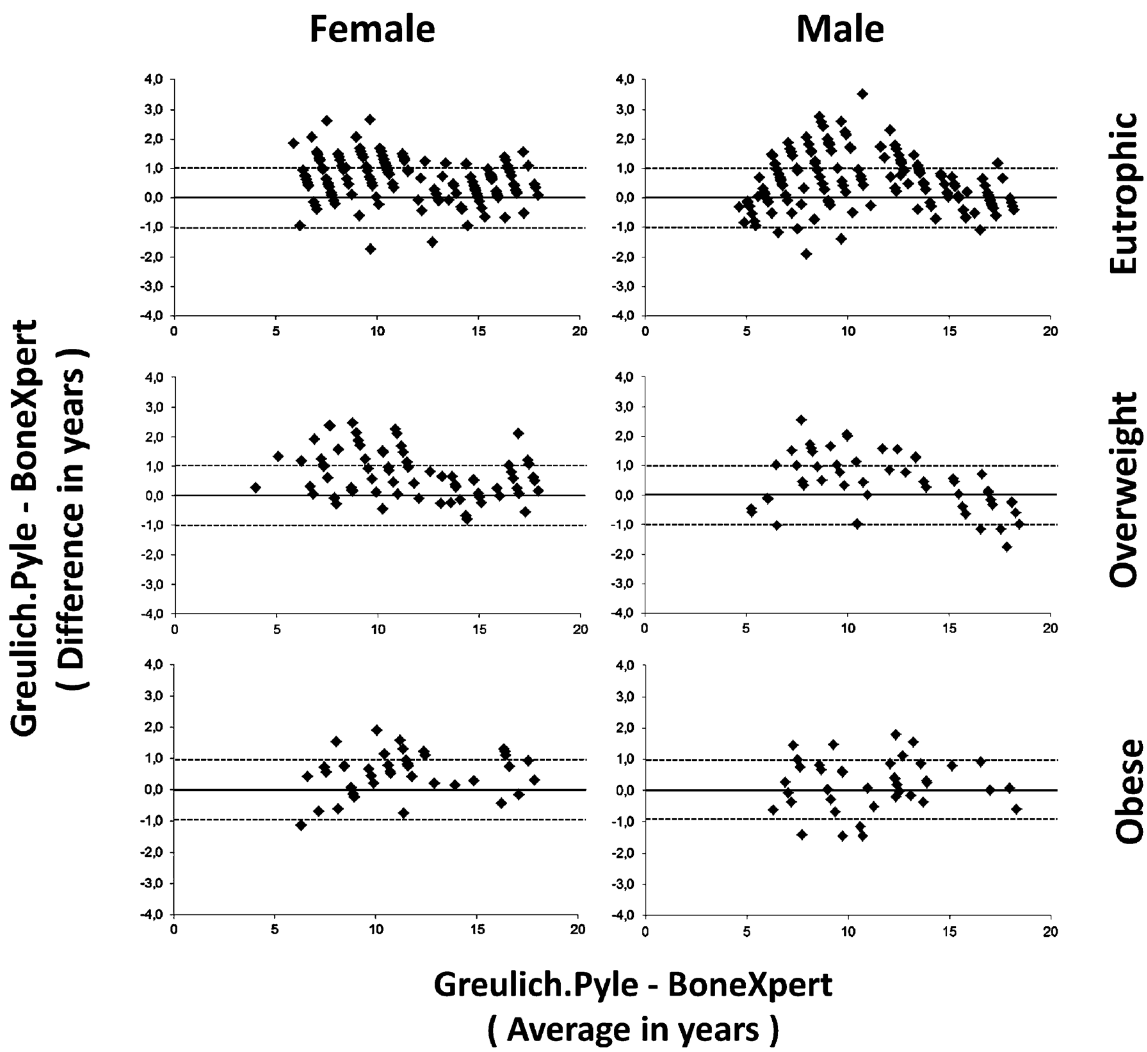

Fig. 2 Bland-Altman plot compares the BoneXpert automated bone age rating and the manual Greulich-Pyle rating in girls and boys with normal weight, overweight and obesity

Discussion

The Greulich-Pyle method has been used for many decades and is considered an important tool to evaluate child and adolescent growth. Despite its wide applicability, the Greulich-Pyle method has been reported as presenting a large interobserver variability [5]. In this study, the bone age reproducibility was low when comparing the rates of the three experts. In contrast, BoneXpert was confirmed to be a highly reproducible observer-independent method.

The comparison between Greulich-Pyle and BoneXpert identified a highly positive correlation between the methods (Pearson's coefficient: r>0.9). As shown by RMSE values, the mean difference between methods varied about 1 year, with higher values observed predominantly in the Greulich-Pyle bone age, which is similar to the Greulich-Pyle interobserver variation [5]. Bland-Altman concordance analysis found the greatest difference between methods at around the age of 10 years. This finding seems to be related to the initiation of puberty and the presence of sesamoid bone. Additionally, overweight girls tend to start puberty even earlier, amplifying this effect.

The potential interference of obesity on bone maturation and growth was previously recognized by other investigators using noncomputerized methods [15–18]. The reported mean bone age advancement varied from 0.6 to 0.9 years for overweight boys and girls. In our study of overweight patients, the findings observed in girls similarly increased, but not in boys, in whom the mean bone age advancement was only 0.3 years. In obese boys and girls, the literature reported mean bone age advancement varied from 1.1 to 1.5 years, similar to our finding of 1.2 years in obese boys and 1.6 years in obese girls. As shown in Fig. 1, some obese patients can present even more than 3 years of bone age advancement, representing the combination of obesity-induced bone age and pubertal anticipation. To the best of our knowledge, no previous study has employed the computer-automated method to determine bone age in obese or overweight children and adolescents. In this study, one of the main new aspects observed is that bone age advancement in obesity is identified both by the Greulich-Pyle method [16–18] and by the computerized method. BoneXpert method is influenced by obesity to a lesser extent than the Greulich-Pyle method. Therefore, in overweight and obese patients, the lower bone age advancement detected by BoneXpert was able to reduce the source of interference when the computerized method is employed.

One of the main factors determining this difference between Greulich-Pyle and BoneXpert in peripubertal ages (10 years) is that computer-automated analysis does not use the presence of sesamoid bone for bone age rating [13]. When rating the bone age by the Greulich-Pyle method, there is a trend to overestimate bone age by the identification of sesamoid calcification, reporting the bone age rating to the next developmental stage. This can be avoided by looking at the full hand bones' developmental stage.

One other factor generating differences between the Greulich-Pyle and BoneXpert ratings seems to be the delay in carpal bones, predominantly observed in younger boys (5–7 years old) with constitutional delay of growth and puberty. This constitutional variation impacts the Greulich-Pyle method, but it does not affect the BoneXpert rating as it does not read carpal bones for bone age determination. In addition, in boys with constitutional delay of growth and puberty, there is nonsynchronous carpal bone development, adding subsequent discordance to the Greulich-Pyle interpretation [19].

One of the limitations of this study was the absence of data on concomitant genital Tanner stage as the majority of participants were evaluated during school activities rather than during a clinical evaluation. Another limitation is that the sample was obtained from a single city, but we would like to emphasize that the population living in Sao Paulo city is around 14.7 million, and very heterogeneous regarding ethnicity and state of origin, therefore being a representative sample of the whole country.

Conclusion

This study describes the effect of obesity and overweight on bone age rated by the BoneXpert computer-automated method in children and adolescents, and compares the BoneXpert results with those obtained by the traditional Greulich-Pyle method. BoneXpert computer-automated bone age determination method showed a significant positive correlation with chronological age and with Greulich-Pyle bone age, both in the eutrophic group and in overweight or obese children and adolescents. The impact of being overweight on bone age was identified by both methods, but BoneXpert rating is affected to a lesser extent when compared to the Greulich-Pyle method.

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Compliance with ethical standards

Conflicts of interest None

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