

The utility of ultrasonographic bone age determination in detecting growth disturbances; a comparative study with the conventional radiographic technique

Parisa Hajalioghli¹ · Mohammad Kazem Tarzamni¹ · Sara Arami¹ · Daniel Fadaei Fouladi^{2,4} · Morteza Ghojzadeh³

Received: 3 March 2015 / Revised: 10 May 2015 / Accepted: 18 May 2015 / Published online: 31 May 2015
© ISS 2015

Abstract

Objective To test whether the conventional radiographic technique in determining bone age abnormalities can be replaced by ultrasonography.

Materials and Methods A total of 54 Caucasian subjects up to 7 years of age with clinically suspected growth problems underwent left hand and wrist radiographic and ultrasonographic bone age estimations with the use of the Greulich-Pyle atlas. The ultrasonographic scans targeted the ossification centers in the radius and ulna distal epiphysis, carpal bones, epiphyses of the first and third metacarpals, and epiphysis of the middle phalanx, as described in previous reports. The degree of agreement between the two sets of data, as well as the accuracy of the ultrasonographic method in detecting radiographically suggested bone age abnormalities, was examined.

Results The mean chronological age, radiographic bone age, and ultrasonographic bone age (all in months) were 41.96 ± 22.25 , 26.68 ± 14.08 , and 26.71 ± 13.50 in 28 boys and 43.62 ± 24.63 , 30.12 ± 17.69 , and 31.27 ± 18.06 in 26 girls, respectively. According to the Bland-Altman plot there was high

agreement between the results of the two methods with only three outliers. The deviations in bone age from the chronological age taken by the two techniques had the same sign in all patients. Supposing radiography to be the method of reference, the sensitivity, specificity, positive predictive value, and negative predictive value of sonography in detecting growth abnormalities were all 100 % in males and 90.9, 100, 100, and 93.8 %, respectively, in females.

Conclusion The conventional radiographic technique for determining bone age abnormalities could be replaced by ultrasonography.

Keywords Bone age · Radiography · Ultrasonography · Greulich-Pyle

Introduction

Hand-wrist radiographs have been used for over a century to evaluate skeletal maturation. Conventionally, the bone age of a given child is determined by side-by-side comparisons of specific structural findings on wrist-hand radiographs with an atlas containing images of the same structural findings in age- and sex-matched normal children. Then the estimated bone age is compared to the child's chronological age to determine whether the skeletal age is advanced or delayed. It is estimated that abnormal clinical situations in which a bone age appraisal is required occur in 1 out of every 20 children [1].

Because of potential hazards of radiography in children [2], some investigators have used ultrasonography to estimate skeletal age [3–6]. Owing to methodological shortcomings and possibly the effect of ethnic differences, however, the usefulness of ultrasonographic techniques in this regard has

✉ Daniel Fadaei Fouladi
Medicorelax@yahoo.com

¹ Department of Radiology, Imam Reza Teaching Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

² Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

³ Department of Physiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

⁴ Neurosciences Research Center, Tabriz University of Medical Sciences, Imam Reza Teaching Hospital, Golgasht Street, Tabriz, Iran P.O. Box 5166614756

been controversial [3, 7]. In addition, the actual clinical utility of ultrasonographic assessment of skeletal age, i.e., its capability in accurate diagnosis of pathologic bone age deviations, has scarcely been investigated [3].

Thus, the present study seeks to examine the performance of ultrasonographic bone age determination compared to the conventional radiographic method in detecting growth problems in clinically suspected children.

Subjects and methods

A total of 54 Caucasian subjects up to 7 years of age with clinically suspected growth disturbances underwent separate left hand and wrist radiographic and ultrasonographic bone age estimations in a referral teaching hospital during a 33-month study. Cases with radiographic indicators of any hand disease were not included.

Informed written consents were obtained from the participants' parents or legal guardians, and the ethics committee of a local university approved this study.

Standard anteroposterior radiographs of the left hand and wrist were acquired following the instructions of Greulich and Pyle [8]. An experienced radiologist who was unaware of the patients' chronological ages interpreted the results using the Greulich-Pyle atlas.

Within 2 days from the radiographic bone age estimations, all the patients underwent ultrasonographic examination of the left wrist and hand using a standard linear array real-time ultrasound machine (Sonix OP, Ultrasonix, Canada) equipped with a 7.5-MHz transducer. Another experienced radiologist without knowledge of the subjects' chronological age or the results of the radiographic bone age assessments performed ultrasonographic examinations.

Ultrasonographic bone age assessment was carried out in compliance with previous instructions [5, 6]. Accordingly, the ossification centers, which were visualized as hyperechoic spots causing marked acoustic shadowing, were targeted by ultrasonographic scans of the radius and ulna distal epiphysis, carpal bones, epiphyses of the first and third metacarpals, and epiphysis of the middle phalanx. Presence, number, and size of the ossification centers were compared to the Greulich-Pyle atlas.

Because of gender-related differences in the rate of normal skeletal development during early life, the results were reported and compared separately for boys and girls [8].

The study variables were sex, chronological age (CA), radiographic bone age (RBA), ultrasonographic bone age (USBA), the difference between chronological and skeletal ages (CA-RBA and CA-USBA), the difference between RBA and USBA (RBA-USBA), and the difference between skeletal ages ± 2 SD of the differences (RBA-USBA +2 SD and RBA-USBA -2 SD).

Statistical analysis

The Bland-Altman plot was employed to assess the degree of agreement between the two imaging techniques in determining bone age and the number of outliers. A proper linear regression model was used for the assessment of correlation between the two methods and to calculate equations. To determine the diagnostic accuracy of the ultrasonographic approach in detecting growth problems, two methods were used. First, the differences between the calculated skeletal ages and the chronological age were plotted against each other; following a previously established approach [3], the number of cases with the same sign (positive, quadrant II; negative, quadrant III) and with different signs (quadrants I and IV) was determined. Second, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the ultrasonographic technique were calculated assuming the radiographic findings as the true diagnosis of bone age problems. SPSS software version 22.0 (IBM Corp., NY, USA) was used for statistical analysis. A significance level of $P \leq 0.05$ was used.

Results

The study group comprised 28 males (51.9 %) and 26 females (48.1 %) with a mean chronological age of 42.76 ± 23.22 months (range: 3–79) at the time of bone age determination.

The mean values of chronological age, skeletal ages calculated separately by radiography and ultrasonography, the difference between chronological and skeletal ages, the difference between skeletal ages calculated by radiography and ultrasonography, and the difference between skeletal ages calculated by radiography and ultrasonography ± 2 SD of the differences were stratified by the patients' sex and are summarized in Table 1.

There was good agreement between the skeletal ages calculated by the radiographic and ultrasonographic methods in both the male (Fig. 1a) and female (Fig. 1b) groups with only three outliers; two in the male group and one in the female group.

The skeletal ages determined by the radiographic and ultrasonographic methods correlated significantly in both males (R-square: 0.98, $p < 0.001$; Fig. 2a) and females (R-square: 0.96, $p < 0.001$; Fig. 2b). The following equations were calculated between bone ages determined by the two imaging techniques in males and females.

In males: *Radiographic bone age (months) = 1.04 ultrasonographic bone age (months) - 0.96*

In females: *Radiographic bone age (months) = 0.96 ultrasonographic bone age (months) + 0.16*

The deviations of the radiographically and ultrasonographically determined skeletal ages from the chronological age are plotted against each other in Fig. 3.

Table 1 Chronological age (CA), radiographic and ultrasonographic bone ages (RBA and USBA, respectively), the difference between chronological and skeletal ages (CA-RBA and CA-USBA), the

difference between RBA and USBA (RBA-USBA), and the difference between skeletal ages ± 2 SD of the differences (RBA-USBA +2 SD and RBA-USBA -2 SD) in male and female patients

Variables (months)	Groups	
	Males (n=28)	Females (n=26)
CA	41.96 \pm 22.25(7.00 to 79.00)	43.62 \pm 24.63(3.00 to 74.00)
RBA	26.68 \pm 14.08(4.00 to 62.00)	30.12 \pm 17.69(4.00 to 60.00)
USBA	26.71 \pm 13.50(4.00 to 54.00)	31.27 \pm 18.06(4.00 to 64.00)
CA-RBA	-15.29[2.35](-40.00 to 2.00)	-13.50[2.06](-33.00 to 1.00)
CA-USBA	-15.25[2.41](-40.00 to 5.00)	-12.35[1.99](-33.00 to 1.00)
RBA-USBA	-0.04[0.35](-4.00 to 8.00)	-1.15[0.74](-14.00 to 6.00)
RBA-USBA +2 SD	5.88 \pm 1.86(1.92 to 13.92)	4.77[0.74](-8.08 to 11.92)
RBA-USBA -2 SD	-5.96 \pm 1.86(-9.92 to 2.08)	-7.07 \pm 3.76(-19.92 to 0.08)

Data are shown as mean \pm standard deviation or [standard error of mean] (minimum–maximum)

Concordant results, i.e., differences with the same sign (quadrants II and III), were documented in all cases (100 %). Accordingly, normal, delayed, and accelerated bone ages were present in 10 (18.5 %), 42 (77.8 %), and 2 (3.7 %) cases, respectively.

The radiographic and ultrasonographic bone ages were exactly the same in 42 patients (77.8 %), including 24 males (85.7 %) and 18 females (69.2 %). The frequency and extent of different radiographic and ultrasonographic bone ages according to the chronological age groups are shown in Table 2. Different bone ages were most commonly seen in subjects aged over 60 months.

The diagnostic accuracy of ultrasonography in detecting male and female growth disturbances (considering radiography as the method of reference) is summarized in Table 3.

Discussion

Over 50 years ago, Greulich and Pyle (GP) developed a method coupled with an atlas of radiographs of the hand and wrist

[8], which is still the most convenient and extensively used technique for determining skeletal age [9]. This holistic method relies on several maturational indicators representing stages of ossification or bone development for any specific age group [6]. In comparison with more detailed, time-consuming techniques such as the Tanner and Whitehouse method, GP has been found to be more suitable for routine clinical practice [10] and even has been considered the gold standard for bone age estimation [2].

Although this radiographic technique is simple, widely accepted, cost-effective, and relatively safe owing to using an effective dose, the cumulative effect of ionizing radiation on children with high life expectancy has been a source of concern for some investigators [2].

Endochondral ossification beginning with the diaphysis, emergence of epiphyseal ossification centers, formation of the growth plates, and finally epiphyseal fusion are the consequent time points in skeletal maturation that a conventional radiography exploits for bone age determination [11]. These structural changes could also be found readily by ultrasonography in expert hands on the basis of their characteristic

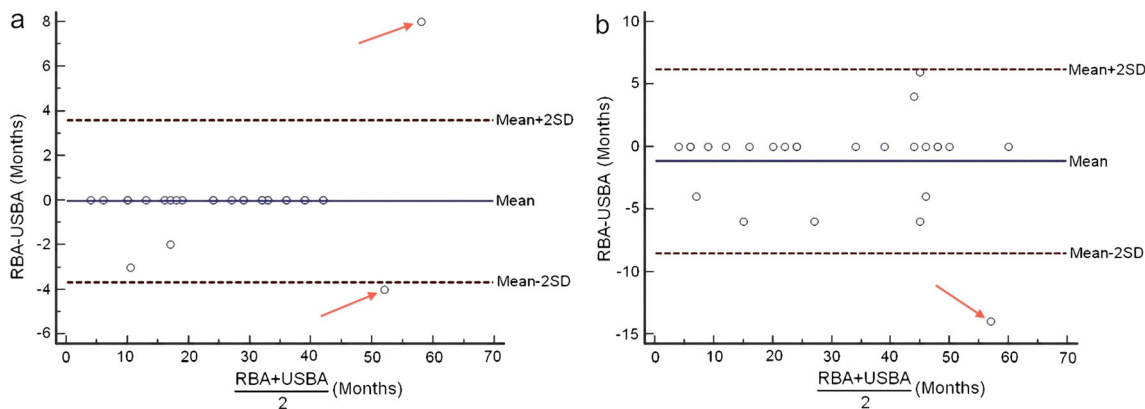


Fig. 1 Difference compared to mean for skeletal age assessed by radiography and ultrasonography in male (a) and female (b) patients. Arrows point to outliers

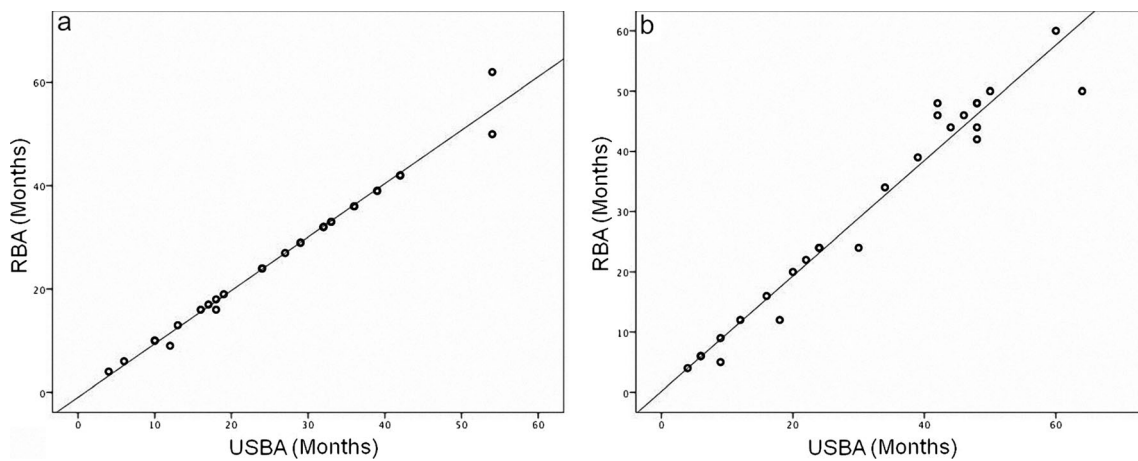


Fig. 2 Scatter plots representing skeletal ages determined by the radiographic and ultrasonographic methods in male (a) and female (b) patients

echogenicity and acoustic shadow. Non-mineralized (cartilaginous) ossification centers are ultrasonographically hypoechoic, and mineralized (bone) tissues are echogenic with acoustic shadows [2].

Ultrasonography is a rapid, safe, and highly accessible technique that provides real-time multiplanar images with the capability of contralateral comparison [6].

Unlike radiography, the absence of ionizing radiation provides a unique opportunity for US examinations to be detailed and prolonged [7].

Using ultrasonography in bone age determination is not a new concept. Previous studies have used the hip [3], iliac and radius bones [4], and ossification foci of the wrist [5] as ultrasonographic landmarks to estimate bone age in children. Some investigators have even introduced non-operator-dependent, specifically designed ultrasonographic devices to automatically determine bone age in children [1, 3]. Many of them,

however, have been found unsuitable for clinical use as replacements for standard radiographic procedures, mainly because of their low accuracy [3, 7].

In the present study we compared estimated bone ages by the conventional Greulich-Pyle method and its ultrasonographic version in a Caucasian pediatric population with suspected growth problems. For both males and females, there were acceptable rates of agreement between the two methods according to the Bland-Altman plots (Fig. 1a and b). Exactly the same estimations were observed by the two methods in 77.8 % of patients: 85.7 % for males and 69.2 % for females.

In a similar study by Bilgili et al. [6], the ultrasonographic version of the Greulich-Pyle atlas was tested for assessing skeletal age in children. On the basis of their suggested hand and wrist ultrasonography charts, they found high correlations between ultrasonographic and radiographic results in both males (71.1 %) and females (84.4 %). They finally proposed their ultrasonographic version of the Greulich-Pyle atlas as a valid alternative to radiography for appraising bone age in children without exposing the patient to radiation.

In a very recent study, Daneff et al. [2] assessed bone age with conventional ultrasonography in healthy infants from 1 to 24 months of age. They finally concluded that conventional ultrasonography is capable of identifying the ossification centers of the hand and wrist and can be utilized as an innocuous follow-up tool for patients with growth problems.

Of note, in both mentioned studies only normal children and infants were examined. Determination of bone age is an important step in the process of investigating children with suspected growth problems, because it acts as a reference point for predicting height in the future [12]. Although the approach of including subjects requiring bone age assessment for probable growth issues may yield a heterogeneous study population, it more closely reflects a real clinical scenario and provides more realistic, applicable information in this regard [7].

Consequential racial and ethnic differences have been reported in terms of the usefulness of the Greulich-Pyle method

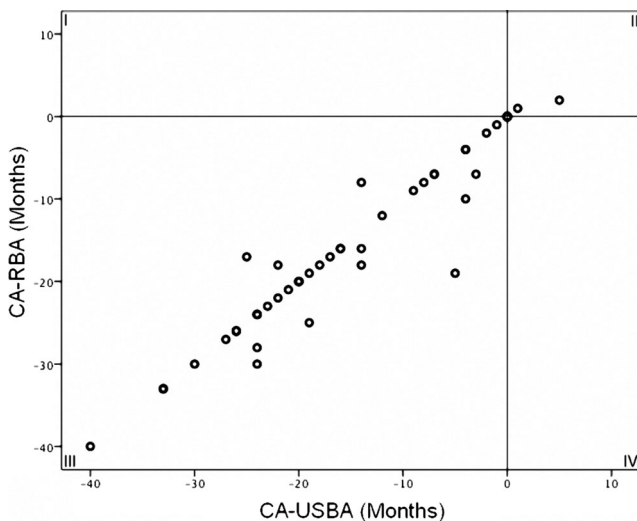


Fig. 3 Plot representing deviations of radiographic and ultrasonographic skeletal ages from chronological age against each other. The error of the two imaging methods had the same sign (positive, quadrant II; negative, quadrant III) in all cases

Table 2 Frequency and extent of different radiographic and ultrasonographic bone ages (RBA and USBA, respectively) according to the chronological age groups

Chronological age groups (months)	No. of patients			Different RBA and USBA no. (%)	Extent of difference (months)
	Males	Females	Total		
≤12	4	4	8	2 (25)	3, 4
>12 and ≤24	3	4	7	1 (14.3)	6
>24 and ≤36	5	2	7	1 (14.3)	3
>36 and ≤48	4	3	7	0 (0)	–
>48 and ≤60	5	4	9	2 (22.2)	6, 6
>60	7	9	16	6 (37.5)	4, 4, 4, 6, 8, 14

in determining skeletal age in the pediatric population [13–19]. In Caucasians, however, the GP atlas has been found reliable and clinically applicable [9, 18, 20]. Thus, in comparison with the reports on non-Caucasians [2, 6], the results of the present work are expected to be more reliable.

Although a difference (Bland-Altman) plot is a very good tool for analyzing the agreement between two different assays [21], it is unable to identify whether two assays tend to err in similar directions for each patient. For bone age determination methods, calculating the difference between skeletal and chronological ages has been suggested to obviate this shortcoming [3]. Our relevant results in this regard were also significantly promising for both males and females as errors with the same signs were found in 100 % of cases (Fig. 3). This is in contrast with the results of Khan et al. [7], who showed that ultrasonography, in comparison with radiography, tended to over-read delayed bone age and underread advanced bone age. It should be noted that they used an automatic device instead of a subjective ultrasonographic assessment in their work, and this may justify the conflicting results between the two studies.

Assuming the radiographic approach as the standard method in determining abnormal bone age deviations in the current study, the sensitivity, specificity, PPV, and NPV of the ultrasonographic technique were high in both males (100 % for all) and females (90.9, 100, 100, and 93.8 %, respectively). These results along with the calculated equations between the radiographic and ultrasonographic methods for bone age estimation (males: radiographic bone age = 1.04 US bone age -0.96; females: radiographic bone age = 0.96 US bone age +0.16) further bolster the suitability of ultrasonography in revealing

growth abnormalities among the Caucasian pediatric population. Although not clinically consequential, different results between ultrasonography and radiography in estimating bone age were higher in patients aged 60 months and older compared to those in the other chronological age groups (Table 2). A higher proportion of female patients in this age group may indicate a less accurate ultrasonographic method in females than in males in detecting growth problems.

Carpenter and Lester [22] concluded that when bone age is determined in children under 10 years of age the entire hand should be considered, and putting too much emphasis on the carpal bones may cause extensive under- or over-readings. Using a balanced approach that includes all bones of the distal part of the upper extremity including the distal radius and ulna, carpal bones, metacarpal bones, and phalanges has been proposed as an ideal method in appraising skeletal age in children by either radiography or ultrasonography [6]. We also followed a similar approach in the current study.

A rather small sample size might be acknowledged as a limitation in this work. Nevertheless, it should be noted that even in the present form this study managed to adequately verify its main assumption that the conventional radiographic method for determining growth deviations in children can be reliably replaced with ultrasonography. To categorize the results on the basis of chronological age, however, further studies with larger sample sizes are recommended.

Finally, it should be noted that each imaging method (radiography or ultrasonography) has its own pros and cons. Bone-age determination by the conventional radiographic technique, i.e., X-ray of the left hand and wrist (Greulich-Pyle), has been universally used since the 1950s. This method

Table 3 Diagnostic accuracy of ultrasonography in detecting bone age abnormalities in the two genders considering radiography as the method of reference

Sex	No. of patients	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)
Male	28	100	100	100	100
Female	26	90.9(58.7–99.8)	100	100	93.8(69.8–99.8)

CI confidence interval, NPV negative predictive value, PPV positive predictive value

is easily affordable almost everywhere, not costly, very simple to perform, and allows a “second opinion,” since a great majority of pediatric endocrinologists prefer to read X-ray radiographs themselves and therefore rely on their own interpretation to make the ultimate decision.

On the other hand, even if a child has a growth problem detected in the newborn period, since most centers request a bone age determination on a yearly basis, a total of approximately 20 hand and wrist X-rays are expected in the child's lifetime. Therefore, the risk of cumulative ionizing radiation with bone age X-rays is not negligible. Considering this, ultrasonography is a far safer technique, but at the same time it is not as rapid as conventional X-ray imaging of the hand and wrist. It requires a physician trained in ultrasonography, whereas an X-ray can be obtained by a technician. Unless the images and a corresponding atlas are provided, the requesting physicians have to trust the sonologist. In addition, a considerable number of locations worldwide do not have access to ultrasound equipment.

In this study we showed that the conventional radiographic bone age determination method can be reliably replaced by ultrasonography. Now, when both techniques are available, it is up to the requesting physician to weigh the benefits against risks and decide which modality is suitable.

Conclusions

On the basis of our findings, the conventional radiographic technique for determining bone age abnormalities can be replaced by ultrasonography.

Conflict of interest The authors declare that they have no conflict of interest.

References

- Mentzel HJ, Vilser C, Eulenstein M, Schwartz T, Vogt S, Bottcher J, et al. Assessment of skeletal age at the wrist in children with a new ultrasound device. *Pediatr Radiol*. 2005;35(4):429–33.
- Danef M, Casalis C, Bruno CH, Bruno DA. Bone age assessment with conventional ultrasonography in healthy infants from 1 to 24 months of age. *Pediatr Radiol*. 2015.
- Castriota-Scanderbeg A, Sacco MC, Emberti-Gialloreti L, Fraracci L. Skeletal age assessment in children and young adults: comparison between a newly developed sonographic method and conventional methods. *Skelet Radiol*. 1998;27(5):271–7.
- Wagner UA, Diedrich V, Schmitt O. Determination of skeletal maturity by ultrasound: a preliminary report. *Skelet Radiol*. 1995;24(6):417–20.
- Nessi R, Garattini G, Bazzini E, Zaffaroni R, Lazzarini F. [Ultrasonography assessment of ossification foci of the wrist and pubertal growth spurt]. *La Radiol Med*. 1997;94(1–2):43–6.
- Bilgili Y, Hizel S, Kara SA, Sanli C, Erdal HH, Altinok D. Accuracy of skeletal age assessment in children from birth to 6 years of age with the ultrasonographic version of the Greulich-Pyle atlas. *J Ultrasound Med*. 2003;22(7):683–90.
- Khan KM, Miller BS, Hoggard E, Somani A, Sarafoglou K. Application of ultrasound for bone age estimation in clinical practice. *J Pediatr*. 2009;154(2):243–7.
- Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford: Stanford University Press; 1959.
- van Rijn RR, Lequin MH, Robben SG, Hop WC, van Kuijk C. Is the Greulich and Pyle atlas still valid for Dutch Caucasian children today? *Pediatr Radiol*. 2001;31(10):748–52.
- Horter MJ, Friesen S, Wacker S, Vogt B, Leidiger B, Roedl R, et al. [Determination of skeletal age : comparison of the methods of Greulich and Pyle and Tanner and Whitehouse]. *Orthopade*. 2012;41(12):966–76.
- Kreitner KF, Schweden FJ, Riepert T, Nafe B, Thelen M. Bone age determination based on the study of the medial extremity of the clavicle. *Eur Radiol*. 1998;8(7):1116–22.
- Khan KM, Sarafoglou K, Somani A, Frohnert B, Miller BS. Can ultrasound be used to estimate bone mineral density in children with growth problems? *Acta Paediatr*. 2013;102(9):e407–12.
- Koc A, Karaoglanoglu M, Erdogan M, Kosecik M, Cesur Y. Assessment of bone ages: is the Greulich-Pyle method sufficient for Turkish boys? *Pediatr Int*. 2001;43(6):662–5.
- Buken B, Safak AA, Yazici B, Buken E, Mayda AS. Is the assessment of bone age by the Greulich-Pyle method reliable at forensic age estimation for Turkish children? *Forensic Sci Int*. 2007;173(2–3):146–53.
- Patil ST, Parchand MP, Meshram MM, Kamdi NY. Applicability of Greulich and Pyle skeletal age standards to Indian children. *Forensic Sci Int*. 2012;216(1–3):200 e201–204.
- Hackman L, Black S. The reliability of the Greulich and Pyle atlas when applied to a modern Scottish population. *J Forensic Sci*. 2013;58(1):114–9.
- Zhang A, Sayre JW, Vachon L, Liu BJ, Huang HK. Racial differences in growth patterns of children assessed on the basis of bone age. *Radiology*. 2009;250(1):228–35.
- Moradi M, Sirous M, Morovati P. The reliability of skeletal age determination in an Iranian sample using Greulich and Pyle method. *Forensic Sci Int*. 2012;223(1–3):372 e371–374.
- Zabet D, Rerolle C, Puchoux J, Telmon N, Saint-Martin P. Can the Greulich and Pyle method be used on French contemporary individuals? *Int J Legal Med*. 2015;129(1):171–7.
- Mansourvar M, Ismail MA, Raj RG, Kareem SA, Aik S, Gunalan R, et al. The applicability of Greulich and Pyle atlas to assess skeletal age for four ethnic groups. *J Forensic Leg Med*. 2014;22:26–9.
- Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *Statistician*. 1983;32(3):307.
- Carpenter CT, Lester EL. Skeletal age determination in young children: analysis of three regions of the hand/wrist film. *J Pediatr Orthop*. 1993;13(1):76–9.