PhD. Thesis

Lower Limb and Bone Age Assessment with the EOS System

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University of Pécs,
Medical School,
Pécs
2021

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LIST OF ABBREVIATIONS

AP - Anteroposterior
BA – Bone Age
CA – Chronological Age
CI – Confidence Interval
CT – Computed Tomography
FAA – Femoral Anatomical Axis
FHD – Femoral Head Diameter
FM-FS - Femoral Mechanical Axis - Femoral Shaft [Angle]
FMA – Femoral Mechanical Axis
FNA – Femoral Neck Axis
FNL - Femur Neck Length
FO – Femoral Offset
FT – Femoral torsion/ Femoral Version
FTR – Femorotibial Rotation
ICC – Intraclass Correlation Coefficient
LMA – Lower Limb Mechanical Axis
MR – Magnetic Resonance
NS – Not Significant
NSA – Neck Shaft Angle
mTFA - Mechanical Tibiofemoral Angle
PCL – Posterior Condylar Line
PHV – Peak Height Velocity
SCFE – Slipped Capital Femoral Epiphysis
SD – Standard Deviation
TM – Transmalleolar Line
TMA – Tibial Mechanical Axis
TMAn – Tibial Mechanical Angle
TT – Tibial Torsion
VIF – Variance Inflation Factor
2D – Two-dimensional
3D – Three-dimensional

I. INTRODUCTION

I. 1 The Importance of Assessment of the Lower Limb Biomechanical Parameters

The lower limb plays a vital role in locomotion and balance. A combination of factors influence its function, and the actions needed for upright motion and balance require an interplay between the dynamic elements of the neuromuscular system and the fixed biomechanical parameters ie. the bony skeleton. The lower limb of the developing child and adolescent is constantly changing and if the bony biomechanical parameters exceed the range of normal it can be indicative of a developing disorder or pre-disease state[5,12,52]

Severe alterations in biomechanical parameters can cause significant hardship via pain, gait deviation and even joint luxation. Disorders such as limb length discrepancy and torsional deformities and others have been associated with later osteoarthritis. Futhermore, femoral anteversion, leg length discrepancy and numerous other biomechanical parameters have been positively associated with increased risk of injury during sport and physical activity.

I. 2 Assessment Methods of the Lower Limb

Balancing the needs of the investigation and the radiation burden of the individual is vital due to the debilitating effects of long term exposure to ionizing radiation.

Lower limb assessment typically takes place via physical examination in and imaging. Imaging methods typically include conventional radiography which has a lower cost, but suffers from magnification errors, or CT / MRI, which are may be less accessible, more expensive and associated with higher doses of radiation (CT), in the non-weight bearing position (CT, MR) and children may require sedation or anesthesia.

The EOS 2D/3D scanner is an emerging imaging system capable of performing low radiation, full-length, high resolution imaging of children and adults with images generated from two orthogonal planes in one pass. Three-dimensional reconstructions can then be created allowing automatic measurement of biomechanical parameters of the lower limb.

I. 3 Bone Age

Bone age is a metric that describes the state of maturity of an individuals' skeletal system. By assessing the development of one or more bones, an estimation can be made that may serve as a useful indicator of biological age, and may be compared or contrasted to the chronological age, as described in years, months, weeks, days and hours.

Commonly used bone age methods cannot be applied to EOS images taken with the normal positioning protocol, however, as the raised upper limb position obscures the carpal region (shown in figure 1).

Figure 1. The EOS scanner is a biplanar imaging device with two X-ray sources and detectors. [Image reproduced with permission from eos-imaging.com, Paris, France].

I. 4 Goals of this Study

The study was performed in two parts, and the aims were as follows:

Part 1:

To evaluate the relationship of cervical bone age (using the Hassel-Farman method) and lower limb anatomical and biomechanical parameters in a population 2-24 years old;

Part 2:

To identify and assess other alternative bone age methods for use with the EOS scanner, without the need for changes in position, based on:

a. Reliability;
b. Difficulty of assessment;
c. Time taken for assessment.

PART I - Lower Limb Assessment vs. Bone Age

II.1 MATERIALS AND METHODS

II.1.1 Population

The examined population was formed from EOS images collected in our department over the course of routine clinic practice from 2007-2012. Patient records were reviewed, yielding a total of 7108 image-pairs, of which 3,473 were in the age group 2-24 years old, and individuals were excluded if they were found to show any biomechanical pathology of the lower limb, history of previous surgery of the lower extremity, previous disease affecting growth or any limb/ body asymmetry. Due to a higher number of older adolescent patients collected, image numbers were limited from the ages of 17-24 years old to 50 cases per year (25 males and 25 females) resulting in 400 cases. From the 2360 aged 2-16 years old, 727 remained after the aforementioned exclusion criteria were applied, for a total of 1127 individuals. sterEOS reconstruction failed in 105 and cervical evaluation was not possible in 17, resulting in 1005 cases.

II.1.2 Bone Age Assessment

Cervical bone age assessment based on the morphology of C3, C4 and C5 vertebrae was performed as per the six-stage Hassel-Farman method (described later, in Figure 4b).

II.1.3 Parameters Evaluated

3D-modelling of both lower limbs was performed, and 14 parameters of the lower limb measured (see Figure 2a-k):

1. Femur mechanical axis length/ ‘Femur length’ (Fig.2a);
2. Tibia mechanical axis length/ ‘Tibia length’ (Fig.2a);
3. Lower limb mechanical axis length/ ‘lower limb length’(Fig.2a);
4. Femoral head diameter (Fig.2d);
5. Femoral neck length: the distance between the centre of the femoral head and the proximal diaphyseal axis, as measured along the axis of the femoral neck (Fig.2e);
6. Neck-shaft angle (NSA)/ collodiaphyseal angle (Fig.2f). This is the angle between the axes of the femoral neck and the proximal diaphysis;
7. Femoral offset (Fig.2g): the distance between the centre of the femoral head and the closest point along the axis of the femoral shaft;
8. Mechanical tibiofemoral angle (mTFA)/ ‘hip-knee-ankle angle’ (Fig.2b): the angle between the mechanical axes of the femur (passing from femoral head to the centre of the distal femur) and tibia (passing from the centre of the proximal tibia to the middle of the ankle) in the frontal plane of the knee. By

convention values in the varus position are recorded as negative, and in valgus as positive;

9. Femoral mechanical axis-femoral shaft angle (FM-FS)/ hip-knee angle (Fig.2c): the angle between the mechanical and anatomical axes of the femur in the frontal plane of the knee;
10. Femoral mechanical angle (Fig.2k): angle between the femoral mechanical axis and the axis of the femoral condyles;
11. Tibial mechanical angle (Fig.2k): angle between the tibial mechanical axis and the tibial plateau;
12. Femoral version/ femoral torsion (Fig.2h): angle between the axis of the femoral neck and the posterior condylar line, projected on a plane perpendicular to the mechanical axis of the femur;
13. Tibial torsion (Fig.2j): angle between the transmalleolar and transcondylar axes, projected on a plane perpendicular to the mechanical axis of the tibia;
14. Femorotibial rotation (Fig.2i): angle between the tibia and the posterior femoral condylar line.

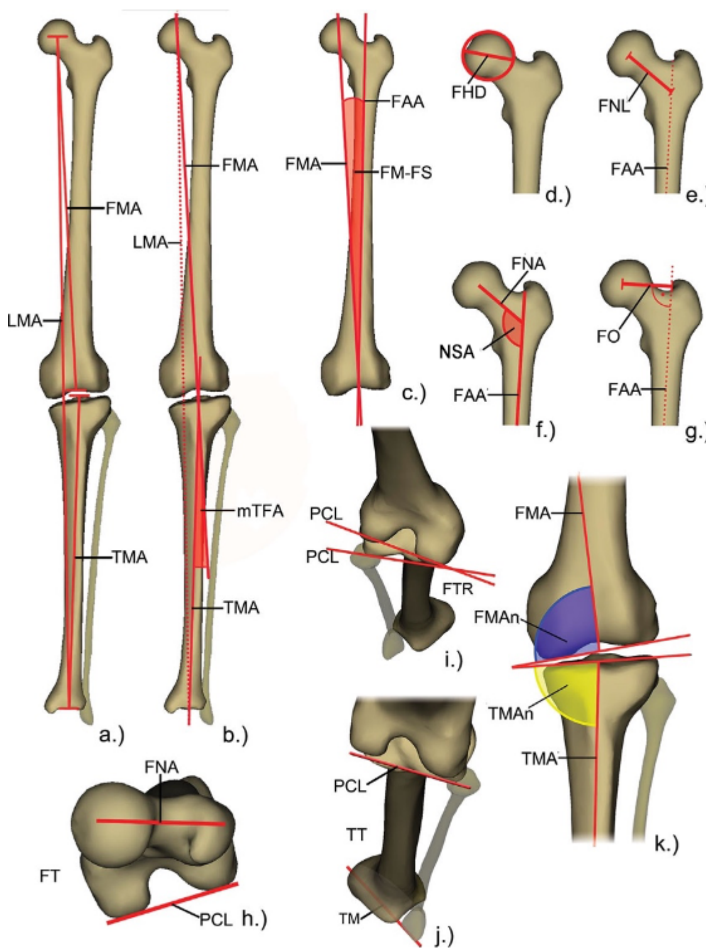


Figure 2. Lower limb parameters measured with the EOS software. NSA, Neck-shaft angle; FAA, Femur anatomical axis; FHD, Femoral head diameter; FMA, Femur mechanical axis; FMAn, Femoral mechanical angle; FM-FS, Femoral mechanical axis-femoral shaft angle; FNA, Femoral neck axis; FNL, Femur neck length; FO, Femoral offset; FT, Femoral torsion/ femoral version; FTR, Femorotibial rotation; LMA, Lower limb's mechanical axis; mTFA, Mechanical tibiofemoral angle; PCL, posterior condylar line; TM, Transmalleolar line; TMA, Tibia mechanical axis; TMAn, Tibial mechanical angle; TT, Tibial torsion. [Image reproduced with permission from Schlégl et al. 2013.]

Lower limb biomechanical values were recorded and their correlations with the calendar age and the cervical bone age were investigated using standard deviation (SD), Spearman correlation analysis and linear regression. Multicollinearity was examined with the Variance Inflation Factor (VIF) test. If VIF was greater than 1, then multicollinearity was said to be excluded, in $1 < VIF < 2$ mild multicollinearity was said to be present but does not significantly influence the results, or the value was over 2 then multicollinearity was deemed incongruent and we rejected the model.

II.1.4 Neck-shaft Angle investigation

After the original lower limb study, a closer look at the neck-shaft angle (NSA) was later performed, however as the EOS software is not recommended for NSA measurement in individuals younger than four, individuals aged 2-3 were excluded from this study (12 individuals). 6 boys and 6 girls from aged 4-9 were randomly selected from our database from 2013 to return the total number to 1005 (449 male, 556 female).

During this investigation mean NSA value and standard deviation (SD) at each chronological age and bone age were calculated and means were compared using independent t-test. The correlation between the NSA value and the chronological age, and the bone age, were each assessed using the Spearman correlation, as above, and linear regression analysis applied. The effect of the NSA on the chronological age and bone age, together and separately, was also assessed using Stepwise Multivariate Regression Analysis as described above.

Gender differences were also assessed using independent t-test and general linear modelling, with gender input as a dummy variable.

II.1.5 Statistical Analysis

For randomization and selection, the RAND.BETWEEN formula of the Microsoft Excel software was used. A p-value <0.05 was accepted as significant.

II.2 RESULTS

II.2.1 Reliability Results with Hassel-Farman Cervical Bone Age Method

The intraclass correlation coefficient (ICC) values for each observer were ‘excellent’ with intra-observer values of 0.959, 0.953 and 0.949. The inter-observer reliability was 0.976.

II.2.2 Lower Limb vs. Chronological Age and Bone Age

Significant correlations were seen between lower limb parameters and chronological age in all metrics ($p<0.05$). A positive correlation, with increasing values in association with increasing age, were seen in height, femur length, tibial length, limb length, femoral head diameter, femoral offset, neck length, tibial torsion, femorotibial rotation and FMFS angle while a negative correlation was seen at NSA, mechanical tibiofemoral angle, femoral mechanical angle, tibial mechanical angle and femoral torsion.

Analysis of lower limb correlation with cervical bone age also yielded significant results in all parameters. In five of the fourteen measured parameters, bone age showed a greater correlation than chronological age, which was small but significant ($p<0.005$). These five parameters were the NSA (-0.164 vs. 0.13), femoral mechanical angle (-0.082 vs. -0.080), femoral torsion (-0.292 vs. -0.153), tibial torsion (0.240 vs. 0.146) and femorotibial torsion (0.345 vs. 0.187).

Calculated linear model data found that femoral mechanical angle, tibial mechanical angle and FMFS angles were best correlated with models based on the chronological age alone. The NSA, mTFA, femoral torsion, tibial torsion and femorotibial rotation however correlated best with mixed models combining both bone age and chronological age. Femoral, tibial and limb length, femoral head diameter, femoral offset and femoral neck length were better correlated with height than either chronological or cervical bone age.

II.2.3 Neck-shaft angle – a closer look

With respect to chronological age, the NSA started at average value 131.89° ± 6.07° at 4 years old and fell thereafter to a mean value of 128.85° ± 4.46° at 16, followed by a slower decrease until the age of 20, with mean value 127.81° ± 3.84°).

Statistically significant differences were found between those children and adolescents with an elevated or delayed bone age compared to those of the same calendar age (see Figure 3). Individuals with a bone age of 2 or more stages above those at the same chronological age had a mean NSA 3.16° higher than their peers ($p<0.001$), while those with a delayed bone age (2 or more stages below their peers) showed an average NSA that was 4.45° higher ($p<0.001$).

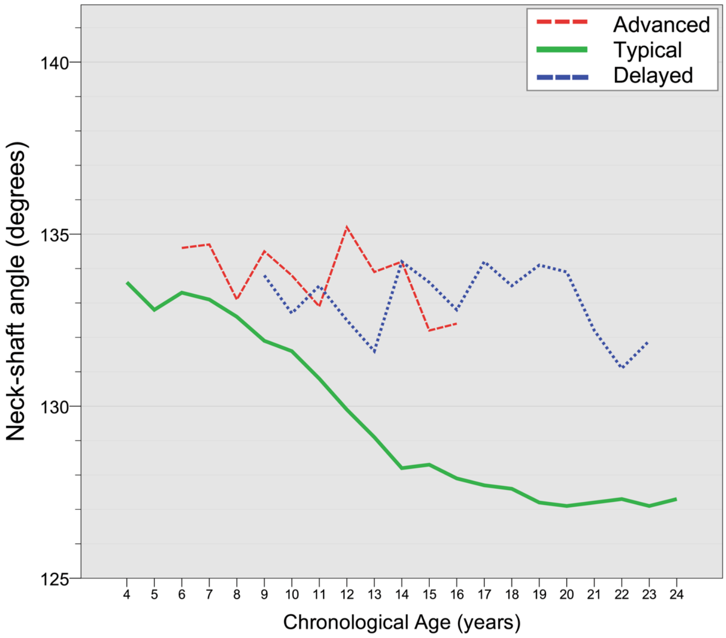


Figure 3. Neck-shaft angle vs. chronological age, sub-stratified by 'delayed' or 'advanced' cervical bone age. Individuals with a 'delayed' or 'advanced' bone age (≥ 2 bone age stages from the 'typical' stage seen by their peers) exhibited significantly elevated neck-shaft angles by a mean 4.45° and 3.16°, respectively (p<0.001). [Reproduced from O'Sullivan et al. 2020].

Similarly, chronologically older and younger individuals at each bone age stage showed significantly higher neck-shaft angles compared to the others of the same stage.

Gender

A statistically significant difference in NSA values between males and females was seen in chronological age-based assessment but not in bone age-based analysis, when analyzed by t-test and general linear modelling.

Linear Regression

Analysis by multivariate linear regression found that changes in the NSA were predicted most accurately when a combined model utilizing both chronological and bone age was used (R^2= 0.226, beta-coefficient=-0.322, $p<0.001$, standard error of the estimates (SE)= 3.809, VIF=0.875; vs. univariate linear regression values R^2=0.101, 0.069).

II.3 CONCLUSIONS

II.3.1 Biomechanical and Anatomical Parameters of the Lower Limb

According to our findings, the longitudinal parameters of the lower limb showed a greater correlation with the calendar age than with the bone age. Although bone age also correlated with these features, often exhibiting strong correlations, the chronological age was stronger – notable were the femoral length (CA vs BA ρ = 0.781 vs 0.747), tibial length (0.766 vs 0.673), total lower limb length (0.763 vs 0.582) and femoral neck length (0.703 vs 0.691).

In contrast to the longitudinal features, rotational/torsional parameters were found to have a stronger Spearman correlation to cervical bone age than the chronological age (Table 5). 'Rotational' parameters were femoral version (CA vs BA ρ= -0.153 vs. -0.292), tibial torsion (0.146 vs. 0.240), femorotibial rotation (0.187 vs. 0.345) and femoral mechanical angle (-0.080 vs. -0.082, N.S.).

Reasons for the closer correlation of rotational parameters to the bone age were not clear. However, as the developmental of rotational features is influenced by muscle contracture, it might not be surprising to see this stronger correlation. Indeed, as epiphyseal plates close during development, the force from the muscles is transmitted to a progressively more rigid bony structure, and hence there is a progressive decrease in flexibility within the bone and across the epiphyseal plate, such that more permanent remodelling takes place, manifested as increased rotation.

Linear models using stepwise regression, found that mixed models combining both bone age and chronological age showed the highest correlation coefficients for the rotational parameters of femoral torsion, tibial torsion and femorotibial rotation (and also the mTFA and NSA).

II.3.2 Neck-shaft Angle

With respect to chronological age, the NSA started at average value 131.89° ± 6.07° at 4 years old and fell thereafter to a mean value of 128.85° ± 4.46° at 16, followed by a slower decrease until the age of 20, with mean value 127.81° ± 3.84°).

NSA values with respect to cervical bone age fell from a mean 130.91° ± 4.26° at stage 1 to 128.07° ± 3.36° by stage 6.

In addition to the small but stronger correlation seen between NSA and bone age (-0.164 vs. -0.130), univariate linear regression found statistically significant models with bone age exhibiting a slightly higher R^2 value (R^2= 0.101 vs. 0.069, beta-coefficient -0.286 vs. -0.264, standard error of the estimate 4.001 vs. 4.176, respectively.

The majority of children at a similar chronological age presented were found to have similar bone age stages. However within each age-year there was a sub-group of children who had a higher or lower bone age compared to their peers. We termed these as ‘slow-maturing’ and ‘fast-maturing’ groups, and the mean NSA of these individuals was significantly higher than their peers, irrespective of whether the child/ adolescent was slow-maturing or fast-maturing. (On average 3.16° and 4.45° higher than their peers, respectively) (See Figure 2). An elevated NSA in less mature individuals might be expected as the value is typically understood to fall with increasing development, however an elevated NSA in those with a higher bone age has not been previously reported.

Our findings led us to hypothesize that femoral neck development may possess a period of susceptibility during which biomechanical forces can act on the proximal femur to determine the angle of the femoral neck. According to this concept, neck angle morphology is an inverse product of ‘force x time’. A shortening of this susceptibility period, as may occur in ‘fast-maturers’, would result in a higher NSA as the cartilage ossifies earlier, before the neck has declined completely from the immature valgus configuration. It is not clear whether these fast-maturing individuals will later undergo a ‘catch-up’ decrease in NSA value or will remain with higher values. Without a longitudinal study, however, it is not possible for us to clarify.

PART 2 - Alternative Bone Age Assessment

III.1 MATERIALS AND METHODS

III.1.1 Population:

The studied population was based on that described in the Materials & Methods section of Part 1 'NSA Assessment Population'. Due to the time differences and server transfers between parts of this study, 59 individuals' scans were lost to the study. As a result, during bone age assessments of the 4-24 year-old population, the total population was 934 individuals.

III.1.2 Literature Review

A literature review was conducted on March 30 2016 from 185 different methods, 6 promising methods entered pilot study (figure 4):

1. Calcaneus (Nicholson 2015);
2. Cervical vertebrae (Hassel & Farman 1995);
3. Shoulder (Shaefer et al. 2015);
4. Hip (pelvis and proximal femur) (Acheson 1957);
5. Iliac apophysis, Risser 'plus' method (Negrini et al. 2015);
6. Knee (O'Connor et al. 2008).

After pilot study, the shoulder method was excluded leading to 5 methods, which were assessed based on:

a. **Reliability:** 30 images were randomly selected and assessed 3 times by each of the 3 observers, on 3 separate occasions. Intra- and inter-observer reliability were calculated via intraclass correlation coefficient (ICC).

b. **Difficulty of Assessment:** 1-4 Likert scale (1: easy, 2: moderate, 3: difficult, 4: impossible); *(For hip and knee methods, if the sum of any landmarks with any difficulty was greater than 2 or 3, respectively, then the overall image rating was '3' ('difficult').)*

c. **Speed:** Two observers used digital timers with each of the methods during the final 200 of the randomized images, to calculate mean evaluation time.

Part II

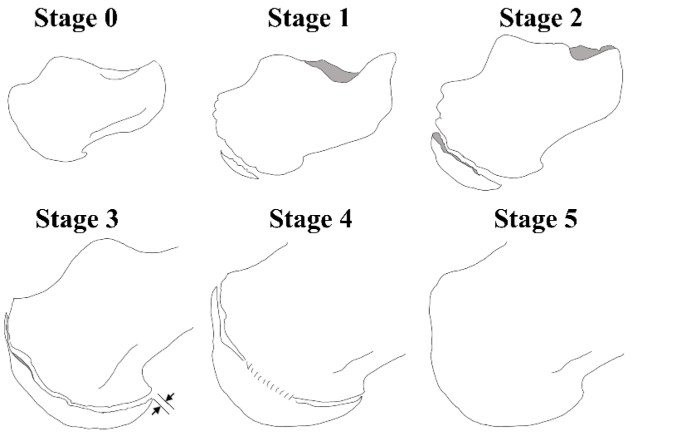


Figure 4.(a) Calcaneus. Adapted from Nicholson et al. 2015.

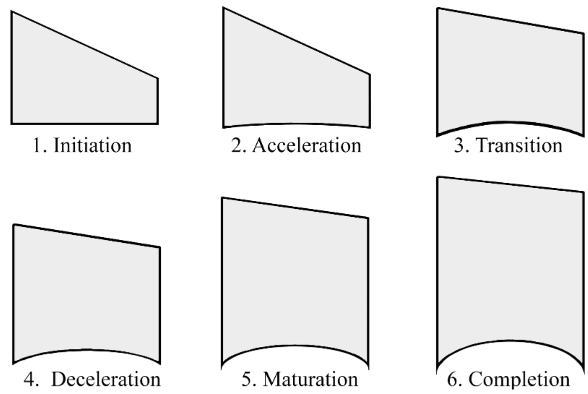


Figure 4 (b) Cervical Bone Assessment as per Hassel & Farman (1995) (Adapted from Schlégl et al. 2017).

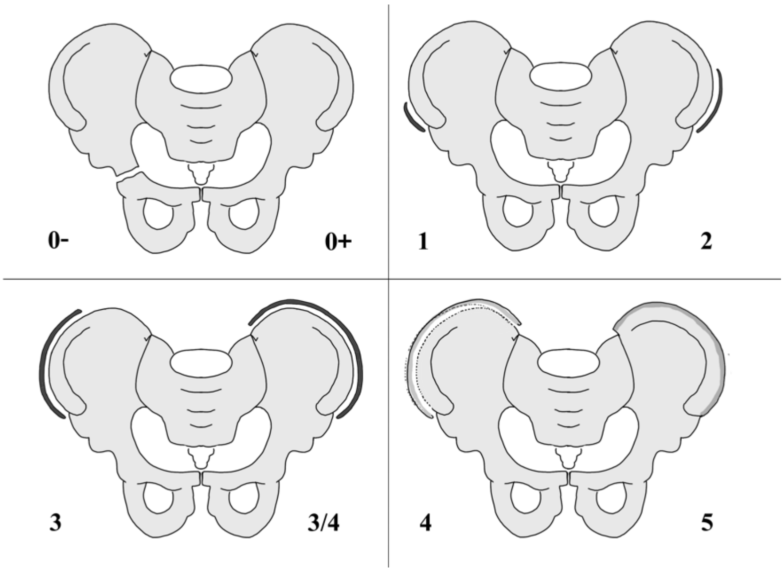


Figure 4 (c). Risser 'Plus' Method as per Negrini et al 2015.

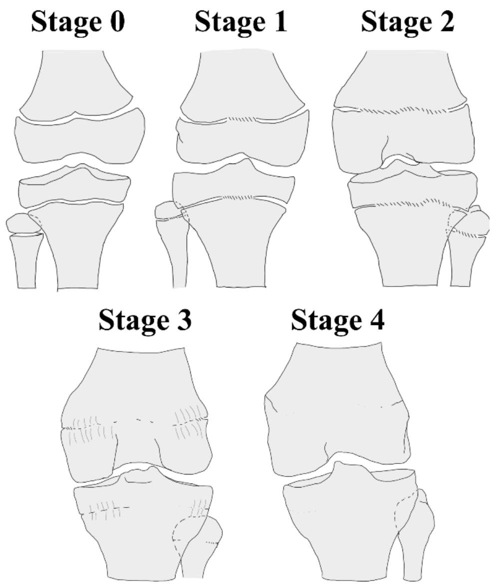


Figure 4 (d) Knee. Adapted from O'Connor et al. (2012)

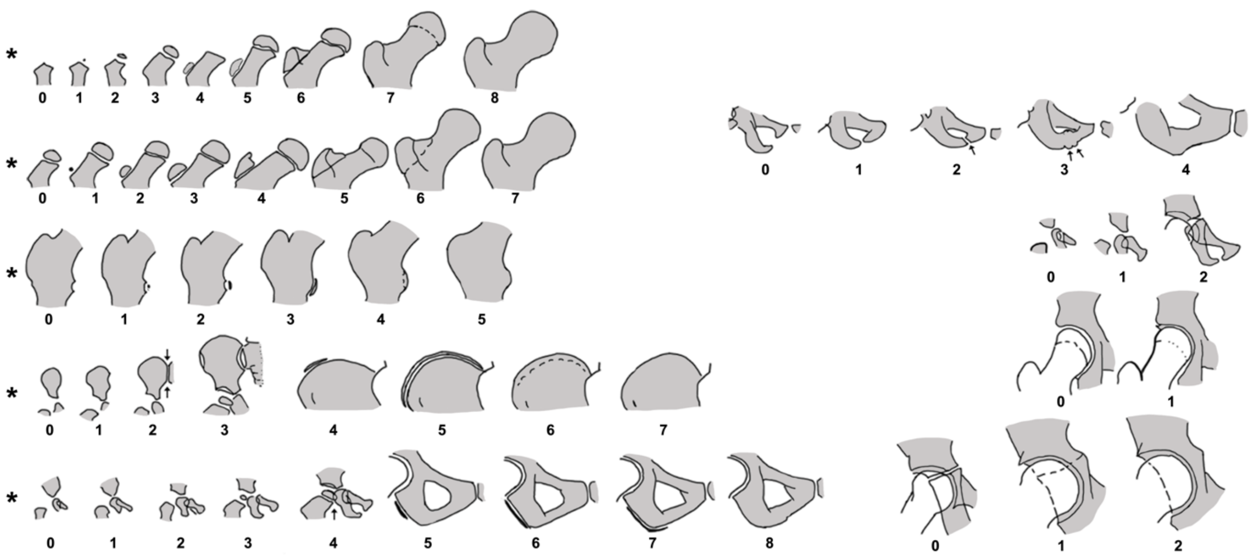


Figure 4. (e) Oxford Hip Method. Adapted from Acheson (1957) The five regions assessed in the abbreviated or 'modified' version of this method are marked with an asterisk (*) (Stasikelis et al. 1996).

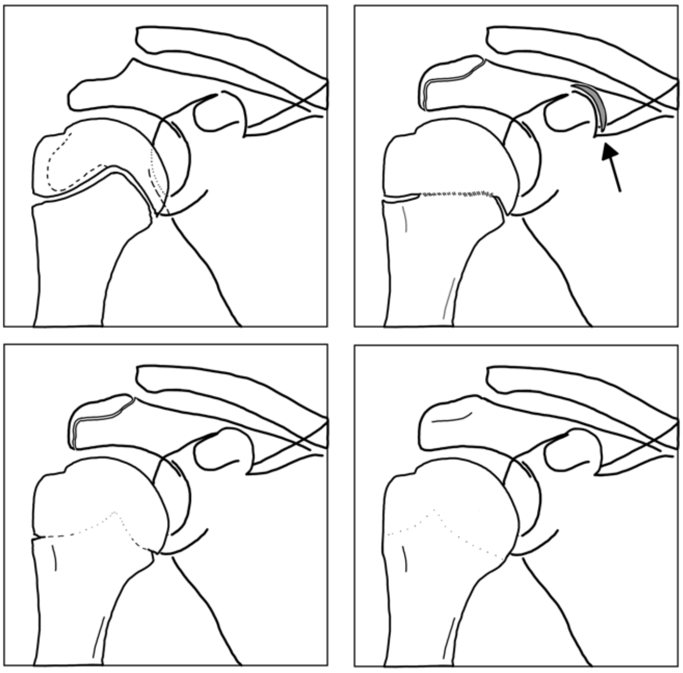


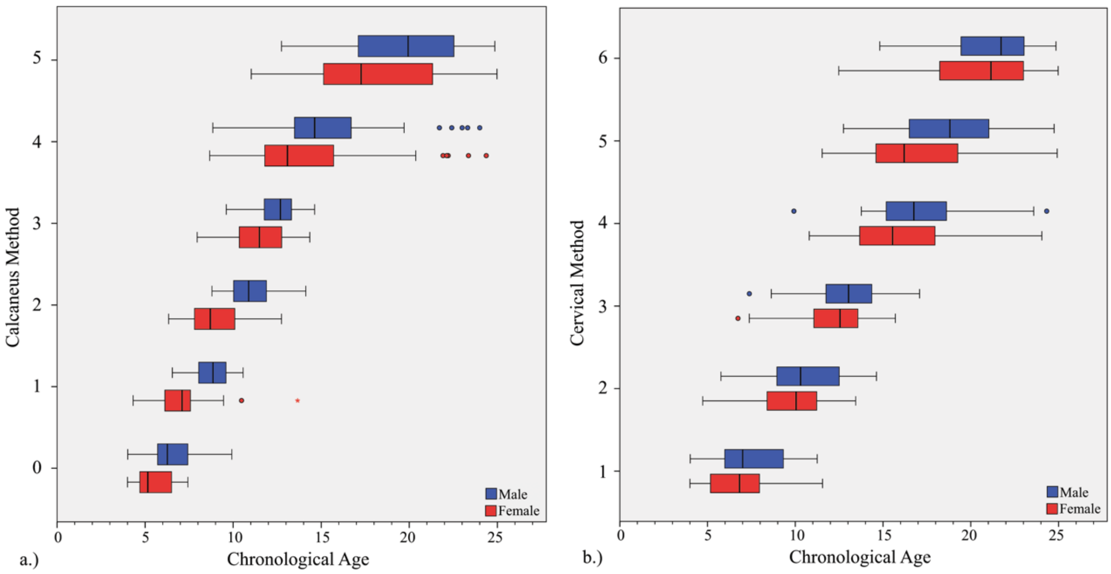
Figure 4 (f). Shoulder (as per Shaefer et al. 2015).

III.2 RESULTS

a. **Reliability:** Excellent values, greater than >0.9 were found for the calcaneus, cervical, Oxford hip and Risser 'plus' methods. The knee method received a 'good' rating of 0.865 for inter-observer reliability and intra-observer values ranged from good (0.841) to excellent (0.956).

b. **Difficulty:** After assessment of all 934 scans, the Risser 'plus' method had the greatest number of 'easy' ratings (89.5%, 836/934), followed by the cervical (79.0%, 738/934), Oxford hip method (78.6%, 734/934), calcaneus (70.8%, 661/934) and the knee (68.2%, 667/934). The calcaneus method could not be applied at all in 6.2% of scans (58/934), followed by 4.2% with the cervical method (39/934), Risser 'plus' and both Oxford hip methods 0.2% of scans (2/934) and finally the knee 0.1% (1/934).

c. **Time:** Shorter evaluation times were seen in methods with fewer stages. With a mean 17.7 seconds, the six-stage calcaneus method was found to fastest, significantly quicker than the second fastest, the cervical method, also a six-stage method, which was found to have a mean of 26.5s per scan (independent t-test, p<0.05). The slowest evaluation time was seen with the Oxford hip method, at times taking more than four minutes – principally due to the nine regions of interest (for a total of 45 stages) which must be evaluated, in addition to uncertainty caused by frequent lesser trochanter visibility problems (see discussion).



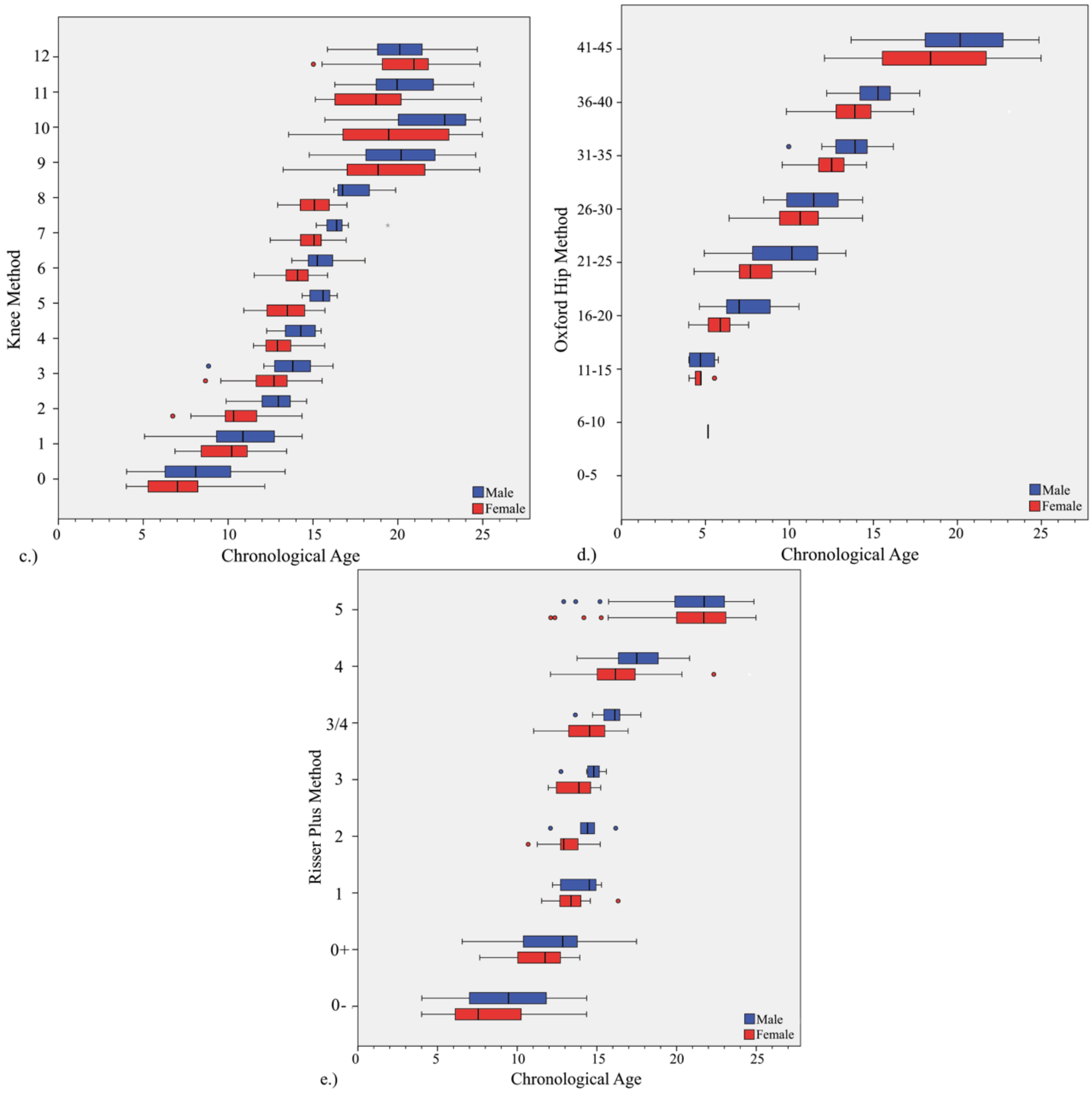


Figure 5 (a-e). Box plot representation of bone age values with respect to chronological age across the 934-individual population (4-24 years old), separated by gender.

Part II

III.3 CONCLUSIONS

III.3.1 Alternative Methods

A. Shoulder

Observers reported problems in assessing one or more landmarks with the shoulder method in 54-62% of scans, especially for identifying fine structure of the apex and angle of the coracoid, so this method was rejected after pilot study. The method recommends use of Y- and axillary views providing additional views when AP views are not sufficient, however these were of course absent from our retrospective series.

B. Calcaneus

Images rated with the calcaneus method received an 'easy' rating in 70.8% (661/934) of scans and 58 of all scans could not be evaluated at all (6.2%). A total of 273 (29.2%) scans were reported to have some difficulty, however 52% (142) of these were specifically a result of the calcaneus lying partially or totally outside of the range of the scan. As the scans were not taken with the intention to investigate foot pathology, the inferior or posterior margin of the scan was calibrated at the discretion of the radiographer or requesting physician in our clinic – as such, difficulties may arise when applying retrospective analysis of bone age with the calcaneus method, however prospective studies could easily employ it by ensuring sufficient image inferior margins (but without any necessary modifications to patient position).

C. Cervical

The Hassel-Farman cervical method received the second highest number of 'easy' ratings 738/934 (79.0%), with just 39 scans unevaluable (4.2%). Overall, problems were most commonly caused by positioning (74 images or 38% of all problematic scans), most typically asymmetrical positioning of the neck and overshadowing of the upper cervical vertebrae by the hands during imaging and technical reasons (57 images, or 29% of all problematic scans) caused by the scan not extending superiorly enough to include the upper vertebrae.

Interobserver reliability values reported with the cervical method were excellent, indeed the highest of all methods (0.976), with equally excellent intra-observer reliabilities from 0.949-0.959. The cervical method was also the second fastest of all methods, at just 26.5 seconds (95% CI 22.16 – 30.75s).

D. Risser 'plus'

The Risser 'plus' system is a unified system made by combining the European and American Risser scales, along with triradiate cartilage assessment. Images rated with the Risser 'plus' system saw the greatest number of 'easy' ratings (89.5%, 836/934 scans) in addition to excellent interobserver (0.94) and intraobserver reliability ratings (0.982 -

0.969). Mean evaluation time was relatively fast at 30.1s (95% CI 27.49-32.71s), likely related to most orthopaedics physician's familiarity with the basics of the method and its' simple well-described stages.

The effect of the inclusion of triradiate cartilage evaluation can be seen in Figure 16. The average age at Stage 0- was 8.69 years and Stage 0+ 11.70 years old in comparison with a mean 9.23 years of age in the traditional Stage 0. A clear difference in sensitivity can be seen by the addition of just one more stadium, as Stage 1 was not seen on average until 13.53 years of age. In line with previous reports, the biggest drawback of the Risser method is Stage 1 arrives after the onset of peak height velocity, greatly limiting its value, whereas triradiate inclusion increases it's potential use.

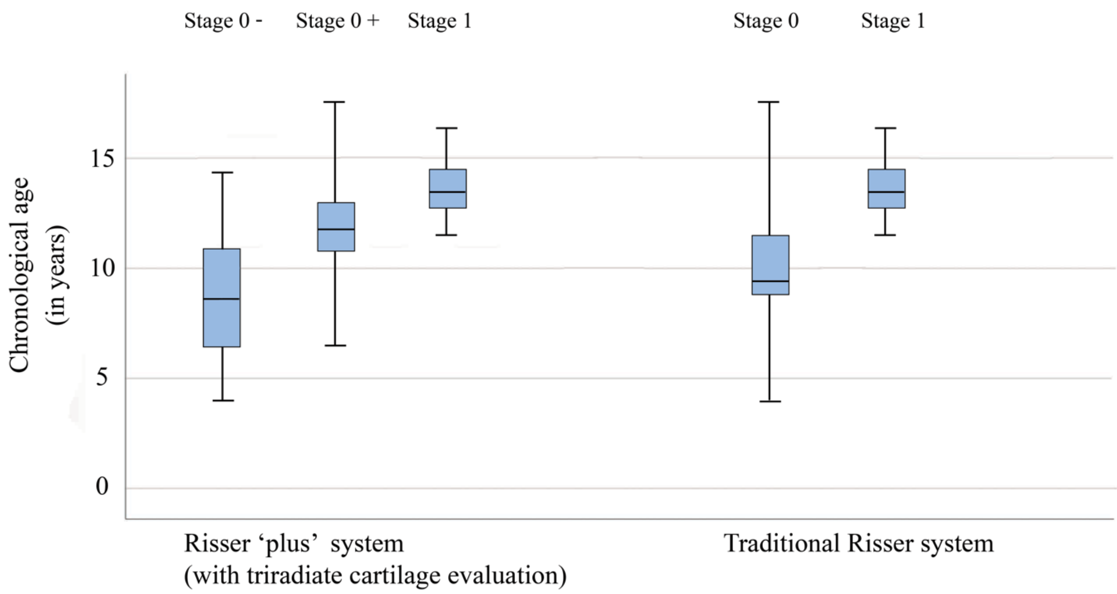


Figure 6. Boxplots presenting the Risser score of children with respect to chronological age of children when evaluated by the Risser 'plus' system and by the traditional Risser system (for clarity of comparison, only the lower Risser scores are shown, see figure 5e for Risser scores 2-5).

The most commonly reported problem with Risser 'plus' evaluation in the study was resolution, seen in 62 (6.6%) images leading to 'moderate' and 'difficult' ratings in 59 and 3 images, respectively. The most common cause was difficulty in the upper stages related to identification of the end of fusion of the iliac crest, and 40 of these images with resolution difficulties were in stages 4 or 5.

E. Knee Method

In the present study, the knee method received the lowest reported number of 'easy' ratings at 68.2% (637/934) of scans. While only 1 scan could not be evaluated, moderate difficulty was reported in 23.7% (221/934) of scans. Overall, problems were most often related to resolution difficulties in identifying the progression of fusion across the margin of the epiphysis and of distinguishing recent fusion with complete fusion (108 or 36% of all problematic scans). These factors also contributed to 'unsure' reports (76 or 26% of all problematic evaluations). Patient positioning associated with shadowing from the contralateral limb further contributed to difficulties (60 or 20% of all problematic scans) which was thought to be influenced by patient step length. Although subjective reports of lower step length causing problems, a Spearman correlation found only a weak inverse correlation (-0.100, $p<0.05$) with ratings. However, step length was found to be significantly lower in image-pairs in which the lateral image could not be evaluated ($p<0.05$, independent t-test).

Inter-observer reliabilities with the knee method were the lowest at 0.865 (albeit still a rating of 'good' by Winer's criteria), intra-observer reliabilities were as low as 0.841 and as high as 0.956. The knee method was one of the slowest methods, at mean 80.9s (95% CI 76.09s – 85.66s).

E. Oxford Hip Method

While just 7.6% (71/934) had 'difficult' ratings and only 0.20% (2/934) of EOS image pairs could not be assessed using the Oxford hip method, this was influenced by the larger number of landmarks to evaluate. As described in the Materials & Methods, difficulty with just one landmark was not recorded as 'difficulty', but rather only if 2 landmarks had some level of difficulty then 'moderate' rating was awarded, and if 3 or more, then 'difficult' rating assigned. However if scans are counted that had any difficulty reported from even one landmark, an additional 334 scans would be included – predominantly due to difficulties assessing the lesser trochanter, which were encountered in 40.9% of all scans (382/934), accounting for 248 (74.3%) of single landmark difficulty scans, but also the ischium (30/334, 8.9%), femur head (15/334, 4.5%) and greater trochanter (15/334, 4.5%).

Our results reporting difficulty in 40.9% of EOS scans would support its omission from evaluation methods as has been previously suggested by other authors. While the relatively high number of stages is advantageous - conferring a finer gradation of maturity and potentially lowering its sensitivity to observer error – multiple landmarks with unique evaluations make the method cumbersome, steepening the learning curve and increasing time required per scan. As a result, the Oxford method was the slowest of assessment systems evaluated, with mean time taken per scan of 82.0s (95% CI 76.12 – 87.88s)

III.3.2 Common problems

Difficulties included: regions lying outside of the image - assessment was difficult or impossible in upper cervical vertebrae (46/934 images 4.9%) and calcaneus methods (144/934 images, 15.4%); position: lower step length was associated with difficult lateral knee assessment & head/hand position with cervical evaluation; and resolution: in the higher stages of the hip, calcaneal and knee methods.

Part II

	Calcaneus	Cervical	Knee	Oxford Hip	Risser Plus
Reliability (Interobs)	· **Excellent (0.945)**	· **Excellent (0.976)**	· Good (0.865)	· **Excellent (0.902)**	· **Excellent (0.940)**
Readability	70.8% of scans easily assessed, 6.2% of scans unassessable · **Image length affected readability**: Image must cover entire length of lower limb or not possible · **Resolution**: can be difficulty distinguishing the timing of end of fusion (stage 4 vs. 5).	79.0% of scans easily assessable · **Image length affected readability**: EOS image must cover entire length of cervical spine or not possible · **Positioning:** (i) Head tilt can lead to mild difficulties. (ii)Hand position can obscure vertebrae making evaluation difficult or position (strict EOS protocol must be applied!)	68.2% of scans easily assessable · **Step length:** can influence readability of lateral radiographs. · **Resolution**: harder to assess features important in more mature stages (trabecular continuity, end of fusion)	78.6% of scans easily assessable · **Complicated:** large number of regions must be evaluated. · **Modified Oxford:** simplified 5-region method may be superior for the clinician – note: omission of lesser trochanter may be required.	· **89.5% of scans easily assessed (highest rated)**
Speed	· **Fastest method** (17.1s)	· Fast (26.5s)	· Slower (80.9s)	· Slowest method (82s)	· Fast (30.1s)
Age Range	· Broad age range: (4.32 - 11.03y)	· Broad age range (4.73 - 13.57y)	· Broad age range (5.07 - 15.02y)	· **Broadest age range** (4.0 - 15.08 y)	· Stages start later than other methods (6.55 - 15.27y)
Other	· **Simple & Easy to learn** · High rater satisfaction	· High rater satisfaction	· Low rater satisfaction	· High rater satisfaction though time consuming.	· High rater satisfaction · **Familiar to orthopaedists**

Table 1. Summary of main features of each bone age assessment method based on results of evaluation in 934 individuals 4-24 years old.

IV. SUMMARY OF THE THESIS

Bone age is a metric describing the progression of a child towards skeletal maturity, and reflects the state of epiphyseal and/or apophyseal development rather than merely the passing of years and months. The biomechanical parameters of the developing lower limb play an important role in normal function and their alteration may be a component or cause of disease or pre-disease states, such as limb length discrepancy, gait deviation and torsion, however reference values are typically compared to chronological age alone.

The EOS scanner has shown an increasing role in paediatric orthopaedics over the past decade due to its' capability for high accuracy, full-body imaging with a low radiation dose burden, however bone age assessment of the hand-wrist cannot be performed without modification of body position, which likely affects spinal posture.

In this study, we aimed to retrospectively assess 15 lower limb parameters of 1005 children aged 2-24 years old and evaluate the correlations with cervical bone age in addition to chronological age, using a large EOS database.

Additionally, our goal was to identify and assess alternative bone age methods that can be applied to EOS images, without the need for modification to the positioning protocol.

Summary of Novel Results and Statements:

1. The lower limb parameters and cervical bone age were assessed in a population of 1005 individuals aged 2-24, the largest reported population to be found in the literature.
2. The Hassel-Farman cervical bone age method was applied for the first time in EOS images. This method was found to be effective and showed excellent inter- and intra-observer reliability values.
3. Some biomechanical parameters were found to be associated with the cervical bone age more than the chronological age – the femoral version, tibial torsion, femorotibial rotation, and neck-shaft angle.
4. Neck-shaft angle decreases with increasing maturity, which we first measured at 131.89° ± 6.07° at 4 years old, falling to mean 127.81° ± 3.84° at the age of 20, in contrast to that still reported in some Anatomy textbooks.
5. Combining cervical bone age and chronological age assessments during neck-shaft angle assessment revealed that those with bone ages >1 stage higher or lower than those of similar chronological age, showed significantly higher neck-shaft angles (3.16° and 4.45° higher, respectively), a novelty in the literature.

6. Furthermore, combined cervical bone age and chronological age assessments of neck-shaft angle assessment were found to correlate greater with neck-shaft values and remove gender difference.
7. The bone age was measured with multiple methods in a large population of 934 individuals aged 2-24 years old.
8. Five methods were found to be applicable to EOS images– cervical, Risser ‘plus’, Oxford hip, calcaneus and knee methods.
9. Bone age evaluations can be performed on EOS scans without the need for further scans, reducing radiation dose and administrative & financial burden on the health system and family.

Publications related directly to the thesis:

O'Sullivan IR, Schégl ÁT, Varga P, Than P, Vermes C. Femoral neck-shaft angle and bone age in 4-to 24-year-olds based on 1005 EOS three-dimensional reconstructions. *Journal of Pediatric Orthopedics. Part B*. 2020 Jul 17 *(online ahead of print)*. **IF: 0.832, SJR: 0.41 (Q2).**

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O'Sullivan IR, Schégl ÁT, Varga P, Than P, Vermes C. Alternative Methods for Skeletal Maturity Estimation with the EOS Scanner – Experience from 934 Patients; Submitted for Publication.

Presentations – International

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O'Sullivan I, Schlégl ÁT, Varga P, Than P, Vermes C. The Correlation Between Collodiaphyseal Angle And Bone Age Based On 1005 EOS 3D-Reconstructions.18th EFORT Congress, Vienna, May 30- June 1, 2017. Programme p 131.

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Presentations – National

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Schlégl ÁT, **O'Sullivan I**, Varga P, Than P, Vermes C. Bone Age - A potential indicator of lower limb's anatomical and biomechanical parameters – 17th EFORT Congress, Geneva, 1- 3. June 2016.

Acknowledgements

I warmly thank my supervisors Prof. Péter Than and Dr. Csaba Vermes for their guidance, support, leadership, patience and advice. For not keeping the leash too tight, but giving me the opportunity to carry out this work. I am truly grateful.

I wish to thank Dr. Ádám Schlégl for his indescribable energy, talent, professionalism and work ethic. Without his initial work and ideas this project could never have started and without his advice, support and patience this would never have had a hope of coming to life and I owe him much.

I am thankful for Dr. Péter Várga for his work on this project, in planning, concepts and performing measurements which contributed greatly to the study.

Furthermore, Dr. Kamilla Kerekes for her helping bring my research into the Hungarian language and Prof. László Poto for his assistance with statistical matters.

I would like to thank the entire staff of the Department of Orthopaedics and the PhD. Office, for welcoming me, assisting me and making it a warm and friendly environment, even for a külföldi, like myself.

I am very grateful to my family for their support, my sister Aisling for her wisdom with numbers and big data, and my dear partner Annamaria for her charisma, uniqueness, nerve and talent.

Kis-Gadóné Wenczler Mária, Németh Tamásné Tímea, and Tamaskóné Sóstai Erika of the Phd Office, without whom I would have been lost at sea! Nagyon köszönöm!

This work was supported by European Grant no. EFOP 3.6.1.-16-2016-00004 for which I am very grateful.

And to Seán – the true engine behind it all, your tireless strength has given me strength. ‘To the victor go the spoils’.