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Distal Femoral Osteochondromas in Patients with Hereditary Multiple Osteochondromas, A Longitudinal Radiological Assessment

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Location where the work was performed:Department of Orthopaedic Surgery, Research school CAPHRI, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands.

Abstract:

Background

The nature of distal femoral osteochondromas in term of size and position in patients with hereditary multiple osteochondromas, (HMO) during skeletal growth has never been assessed before. This study was set up to address three specific aims: 1) to assess whether it is possible to reproducibly measure growth of osteochondromas on plain X-rays, 2) to assess which parameters best describe the relationship between growth of the femur and development of osteochondromas, and 3) to assess whether the osteochondromas' place of origin and its positional relation to the femur changes during skeletal growth.

Methods

Weretrospectively reviewed X-rays of tenpatients diagnosed withHMO, with sixteen individual osteochondromas and measured: length of the femur from the fossa piriformis to the joint line of the knee, distance from the base of the osteochondroma to the joint line of the knee, the base of the osteochondroma, cross section of the femur at the most proximal part of the base and the length of the osteochondroma measured from top to base.Newly formed osteochondromas were registered.Two observers performed all measurements independently.The inter-observer agreement was estimated using concordance correlation coefficients (CCC).

Results

The length of the femur (CCC 0.98 (95%CI 0,97-0,99)) and the height of the osteochondroma (CCC 0.87) could be measured with high reproducibility between individual observers. Measurement of the femoral cross section and the base of the osteochondroma (CCC 0.59 and 0.38 respectively) and the distance of the osteochondroma to the joint line of the knee (CCC 0.43) resulted in low reproducibility. The height of theosteochondroma and the distance to the joint line of the knee increased over time during growth. No newly formed osteochondromas were detected proximal to the existing osteochondromas in the distal femur.

Conclusions

The length of the femur and height of the ostechondromas could bereliably measured on plain X-rays. No new osteochondroma formed proximal to the already existing ones, indicating that they are formed in or close to the epiphyseal line. It seems likely that the osteochondromas are formed at or near the epiphyses during growth and stay in their place of origin, as the femur grows more distal, resulting in a more proximal position of the osteochondromas over time.

Level of Evidence: IV (retrospective case series)

Keywords: *Exostosis, HME, HMO, hereditary multiple exostoses, osteochondroma, growth plate, epiphysis*

1. INTRODUCTION

Hereditary Multiple Ostechondromas (HMO) or Hereditary Multiple Exostoses(HME) is an autosomal dominant disorder known for characteristic growth of osteochondromas[1-4].According to the definition of the World Health Organization (WHO), osteochondromasare cartilage-capped bony outgrowths on the external surface of long bones, consisting of a marrow cavity that is continuous with that of the underlying bone [2, 5, 6].

For a diagnosis of HMO to be made, two or more lesions must be radiographically identified. Osteochondromas typically occur around the metaphysis of long bones and have an incidence of approximately 1 in 50.000 [7, 8]. Onset of HMO may be at any time between early childhood (2-3 years) and puberty with the majority affected during first decade of life [9]. Clinically short stature is considered as a common feature of HMO, with the majority of affected individuals being below average height but within a normal range[4, 10, 11].

Osteochondromas may be sessile or pedunculated and can vary in number and size. They are usually painless and come to clinical attention for cosmetic reasons. Nevertheless large osteochondromas can cause a variety of clinical problems such as pain, bursa formation, fracture after local trauma, or snapping may occur when a large muscles moves over the top of osteochondroma [12]. In addition, osteochondromas on the lower limb can cause various deformities. The most common findings are genu valgum and lower limb length discrepancy[13, 14]. The way in which osteochondromas influence these growth deformities is not clear. Osteochondromas develop when the epiphyseal plate is not yet closed [9, 15] and even though the pathogenesis of HMO has not been completely elucidated,the most adapted hypothesis suggests that the osteochondromas develop in the epiphyseal plate. Nests of cartilage being misplaced fragments of cartilage around the epiphyseal line become isolated on the surface of the metaphysis, proliferate, and form the osteochondroma[16-19]. The periosteum, which is incomplete at the sites of these cartilaginous nests, fails to remodel the metaphysis in a normal manner [16]. If the osteochondroma is formed near the epiphysis we can assume that the growth deformities arise because osteochondromas influence the epiphysis either in a mechanical or a biochemical manner. Because most osteochondromas in HMO occur in the distal femur this is a logical site to investigate the influence of osteochondromas on growth. The nature of distal femoral osteochondroma in term of size and position during skeletal growth has to our knowledge not been assessed up until now. Therefore the aim of this study is to analyse the development of the osteochondromas of the distal femur and to compare their growth to the growth of the distal femur. Since osteochondromas are formed near the epiphysis it is hypothesized that the osteochondromas form near the epiphysis and continue to grow while the femur is growing and therefore the osteochondromas stay in their place of origin. In this manner new ostoechondromas can only form closer to the epiphyseal plate than already existing ones.

This study was set up to address three specific aims: 1) to assess whether it is possible to reproducibly measure growth of osteochondromas on plain X-rays, 2) to assess which parameters best describe the relationship between growth of the femur and development of osteochondromas, and 3) to assess whether the osteochondromas' place of origin and its positional relation to the femur changes during skeletal growth.

2. PATIENTS AND METHODS

Ten patients were selected for this study out of a population of fifty-threepatients with HMO in the age below 20 years from a HMO study population of two medical centres in the Netherlands (OLVG, Amsterdam and MUMC+, Maastricht). Inclusion criteria were at least 3 calibrated anterior-posterior (AP) long standing X-rays of either one leg or both, taken at different time points. Two or more of these X-rays should been taken when the epiphysis was still open. Furthermore, patients should haveat least one lateral knee radiograph in order to determine the direction of the osteochondroma in a three dimensional plain. Immeasurable osteochondroma or technical improper X-ray resolution were considered exclusion criteria.The ten selected patients (12 legs) accounted for 16 osteochondromas that were included in this study.The radiological measurements were performed by two clinicians (HS and WN; orthopaedic surgeons)independently from each other. All measurements were performed on digital calibrated x-rays with digital measuring software. All X-rays were successivelyanalysed per patient.

The following measurements were performed as shown in Figure 1a and 1b (Figure 1ab):

A. Length of the femur from the fossa piriformis to the joint line of the kneein (mm)
B. Distance between base of the osteochondroma and joint lineof the knee(mm)
C. Cross-section of femur (outside of medial to lateral cortex, perpendicular to the joint line) at the most proximal part of the base (mm).
D. Length of the base of the osteochondroma(mm)
E. Height of the osteochondroma from the centre of the base to the top(mm)

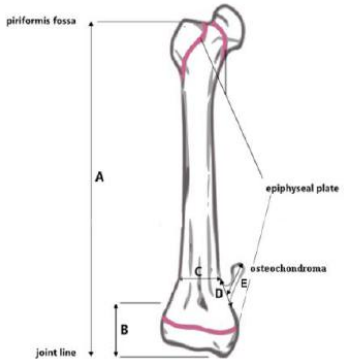


Figure1a. *Schematic figure of the measured parametersonthe X-ray of a femur with a distal* osteochondroma:

A. Length of the femur from the fossa piriformis to the joint line of the knee
B. Distance between base of the osteochondroma and joint line of the knee
C. Cross section femur at the most proximal part of the base
D. Length of the base
E. Length of the osteochondroma

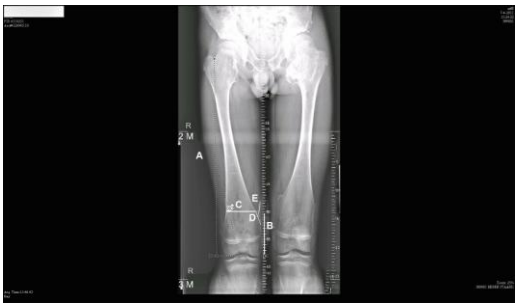


Figure1b. *Representation of thesame measured parametersontheX-ray of a femur with a distal osteochondroma*

The length of the femur (A) was measured from the fossa piriformis to the joint line of the knee in order to measure only the growth of the distal epiphyses. The distance of the osteochondroma base to the joint line of the knee (B) was measured to determine the location of the osteochondroma on the femur during growth. Besides the measurements A-E, all radiographs were checked for occurrence of new osteochondromas.

3. STATISTICAL ANALYSIS

Differences in measurements (A-E) between observers were plotted against the average of observers using modified Bland-Altman plots. The limits of agreement (prediction limits for the differences) were estimated using a variance components model in which replicates were linked within subjects across observers.

Subsequently, for each measurement (A-E) the inter-observer agreement was estimated using concordance correlation coefficients. The concordance correlation coefficient (CCC) is one of the most common approaches to assess agreement where the design of the data involves repeated measurements on subjects by multiple observers. The CCC is a standardized coefficient that takes values between -1 and 1, where -1 means perfect disagreement, 0 translates to an independence situation (all the readings are at random), and 1 indicates perfect agreement[20, 21]. Variance components were used to calculate the CCC. Variance and error components were estimated from linear mixed models in which was accounted for all sources of variation. Subject, observer, subject-observer interaction, and subject-age interaction were treated as random factors. CCCs are reported as

point estimates with their 95% confidence intervals. The statistical analyses were performed using R version 3.0.2 with packages'MethComp' and 'cccrm'[22-24].

4. RESULTS

In10 patients (12 legs), 16 osteochondromas were identified and measured. There were 6 males and 4 females. The average age was 11.6 (range 10-14) at the start of measurement.

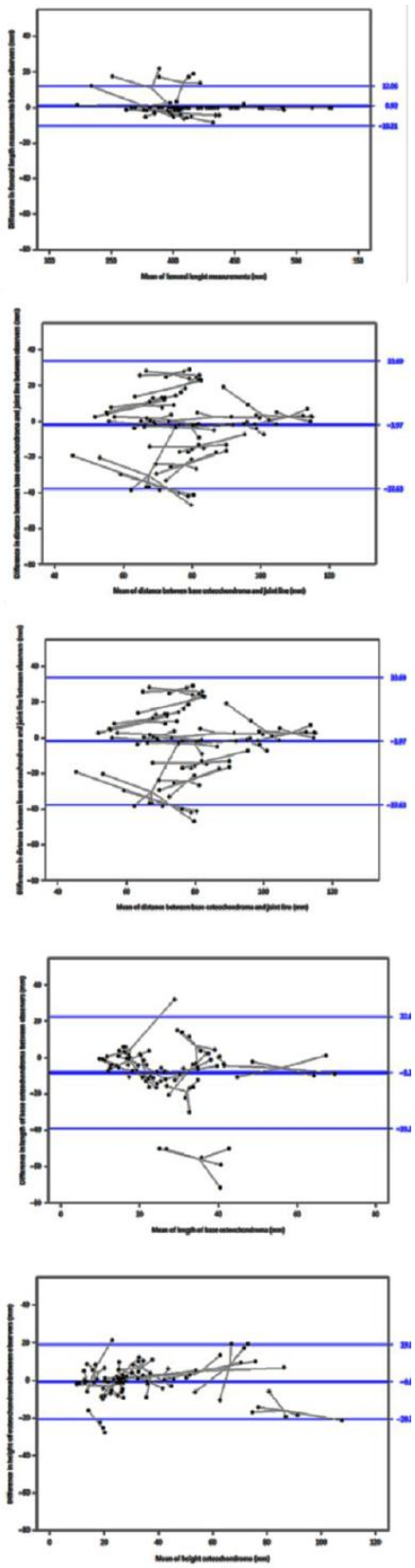


Figure2. *Modified Bland-Altman plots. Differences in measurements (A-E) between observers were plotted against the average of observers. Measurements in time within an osteochondroma are linked with grey lines. Mean differences between observers with 95% confidence limits are shown in blue.*

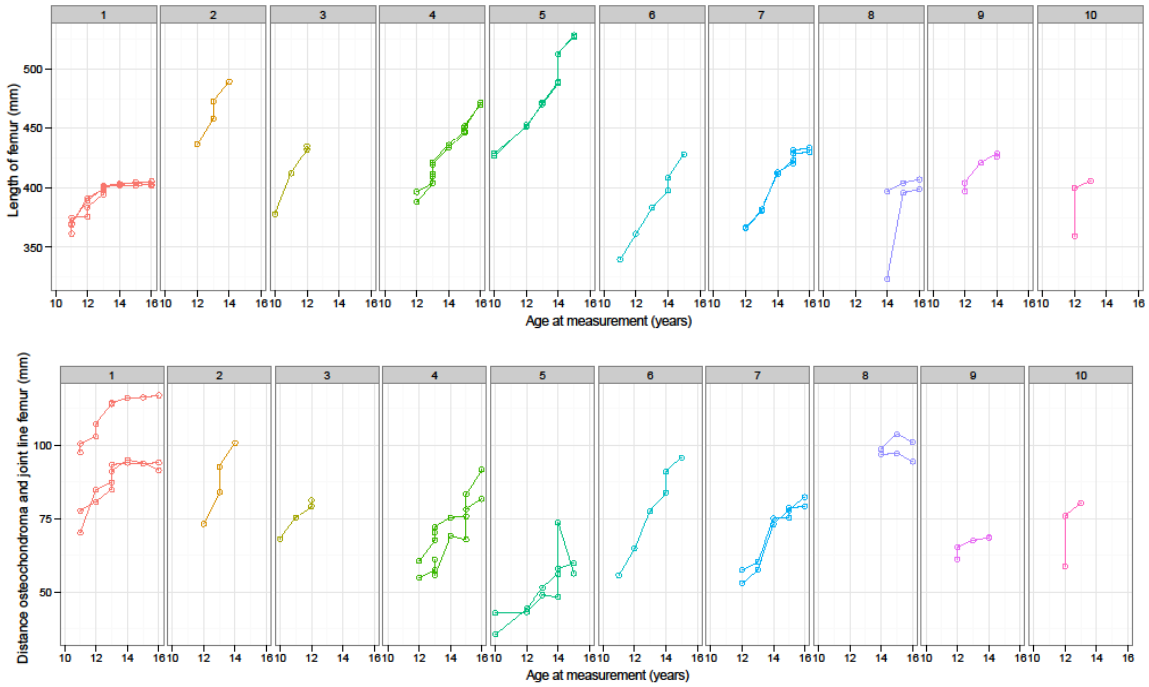
Mean interval between the first and last measurements was 44.4 months (range 22-64 months). In one patient (patient no. 6) the cross section of the femur could not be measured due to anoverprojection of another osteochondroma on the overlying cortex.

Diffeences in measurements (A-E) between observers were plotted against the average of observersusingmodifiedBland-Altman plots (Figures 2A-E). The inter-observerCCCsfortotallength of the femur andheight of the osteochondromawere 0.99 (95%CI 0.97-0.99) and 0.87 (95%CI 0.70-0.94), respectively, indicating a high inter-observerreliabilityforbothmeasurements. Inter-observerCCCsfor cross section of the femur at the most proximal part, base of the osteochondroma, anddistancefrom the base of the osteochondromato the joint line of the femur indicated low inter-observerreliability (0.59 (95%CI 0.23-0.81), 0.38 (95%CI 0.00-0.66), and 0.43 (95%CI -0.01-0.73), respectively).

Both, the total length of the femur and the height of the osteochondroma, could be reliably measured. The length of the femur and the height of the osteochondroma increased over time during growth in all patients (Figures 3A-E). The femoral growth is shown in table 1 (Table 1). The length of the femur increased over time with a varying rate per patient from 3 mm up to 3 cm per year (average 1, 73 cm/year, std. 0,84). The height of the osteochondromas varied widely. The increase in height varied from no growth (or even decrease of height) to 33, 1 mm.

Table1. *Mean results both first and last measurment of the length of the femur and the average growth per year.*

No	Length femur (A) first mm	Length femur (A) last mm	IncreasedLength femur cm/year
1	362,1	405,8	0,89
2	369,5	402,3	0,67
3	369,5	402.3	0,67
4	436,7	490,0	2,4
5	378,8	437,1	3,0
6	392,4	470,9	1,8
7	392,4	470,9	1,8
8	428,1	527,5	2,1
9	428,1	527,5	2,1
10	333,9	432,3	2,2
11	366,5	431,7	1,4
12	366,5	431,7	1,4
13	322,7	397,4	2,7
14	398,9	407,4	0,3
15	388,6	416,5	1,3
16	350,8	408,8	3,0



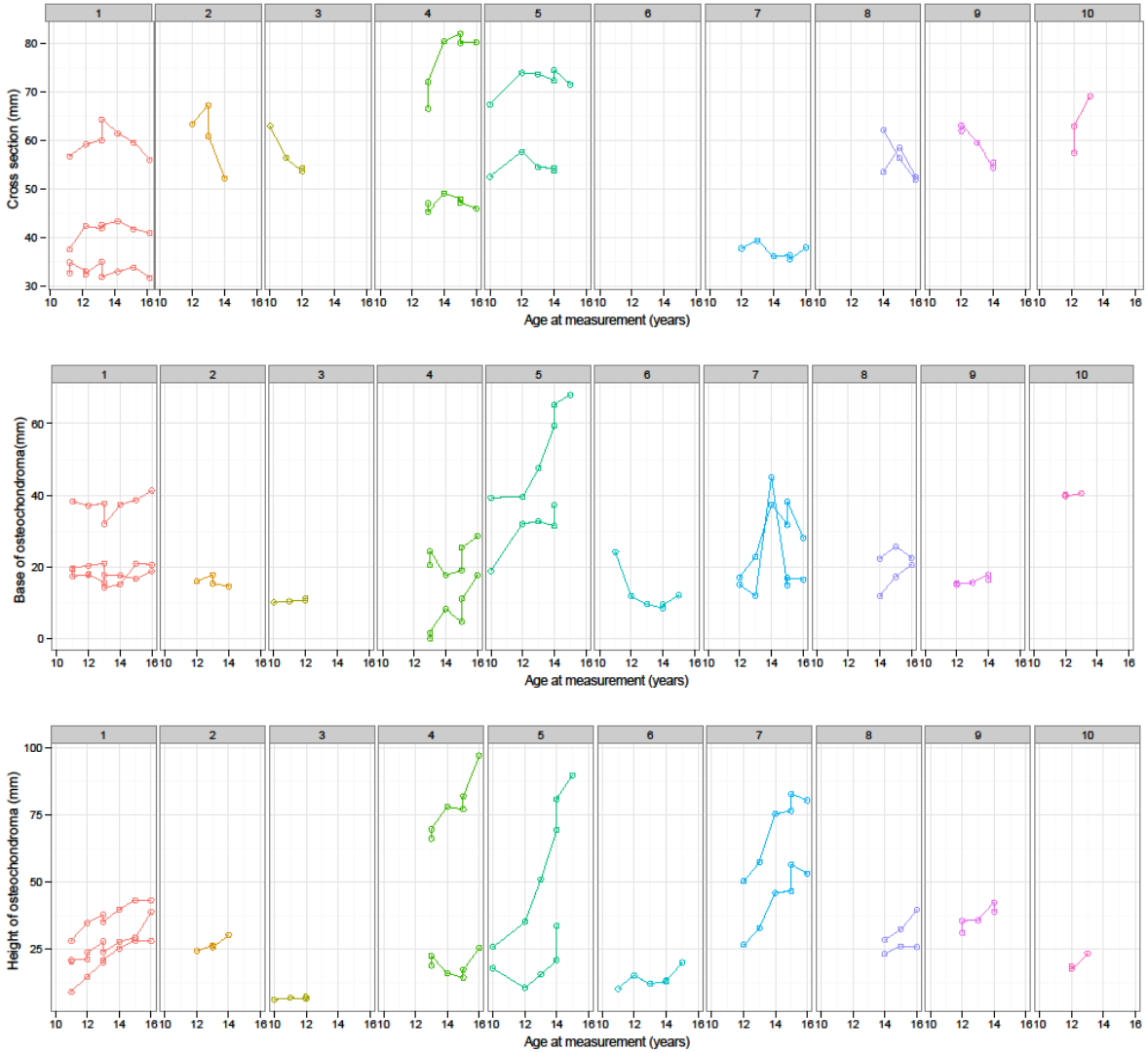


Figure3. *Mean of measurements (A-E) of both observers in time for each patient (1-10). Multiple lines within a patient represent multiple osteochondroma.*

No newly formed osteochondromas were detected proximal to the existing osteochondromasof the distal femur, indicating that all newly formed osteochondromas were formed closer to the epiphyseal line than the already existing ones.

5. DISCUSSION

The aims of this study were to assess whether it was possible to accurately determine growth of osteochondromas on plain X-rays, to assess which parameters best describe the relationship between growth of the femur and development of osteochondromas, to assess whether the osteochondromas' place of origin and its positional relation to the femur changes during skeletal growth. The results indicate that the length of the femur and the height of the osteochondromas could be reliably measured on plain X-rays with high inter-rater agreement. Both increase over time during growth. However measurements of the distance of the osteochondroma to the joint line of the knee, femoral cross section and the base of the osteochondroma resulted in low reliability. Therefore we are unable to provide an answer to the first question which osteochondroma growth parameters best describe the relationship between growth of the femur and development and location of osteochondromas.

The distal femoral growth plate is responsible for 1,4 cm of lengthening of the femur per year in normal femora, as shown by Sissons and Kember[25]. Comparing this normal lengthening of a distal femur to the lengthening of the femur in HMO affected children, it seems that the HMO femora have a slightly faster growing rate (average in this study 1,73cm/year).Several studies show that patients with multiple HMO have shortened long bones[4, 26, 27]. The shortening was proposed to be the result of steal of the longitudinal growth into osteochondromas. Jones et al [27] induced osteochondroma genesis at different time points during skeletal growth in a mouse genetic model and

described that these mice with osteochondromas presented with shorter femora and tibiae than controls. They also concluded that the shortening did not correlate with osteochondroma volumetric growth. Suggesting that even though a steal phenomenon seems apparent, some other unknown mechanism must be contributing to the short bone phenotype.

If steal would influence the growth one would have expected a slower growth rate depending on the distance of the osteochondroma to the epiphyseal line. Unfortunately, the joint line parameters in this study could not be reliably measured; therefore it does not support the hypothesis of a steal phenomenon. Nor does the slightly increased growing rate support this theory.

No newly formed osteochondromasproximal to the existing osteochondroma in the distal femur were observed during longitudinal growth. This confirms the commonly accepted hypothesis that osteochondroma are formed in or near the epiphyses [4, 26, 27].Based on the hypothesis that the distal femur grows distal while the osteochondroma remains in its place of origin we expected that the distance of the osteochondroma to the joint line of the knee would increase over time during lengthening of the femur. Similar we anticipated on the cross section of the femur to decrease due to an increasingly more diaphyseal location of the osteochondroma as the femur lengthens. We cannot verify or reject this hypothesis.

Because the distance of the osteochondroma to the joint line of the knee increased during growth and the new osteochondromas are only formed closer to the epiphysis it is increasing the likelihood that the osteochondromas are formed at or near the epiphyses during growth and stay in their place of origin, as the femur grows more distal, resulting in a more proximal position of the osteochondromas over time.

Some potential limitations of this study should be discussed. First, the studied cohort was small. Second, our study only assessed plain X-rays which were taken according to the local hospital protocol, possibly resulting in small differences in the rotation of the legs that might have influenced the measurements. These influences were noted in the data by for instance a decrease in height of the osteochondroma at a certain time point followed by an increase again in the next time point, however were corrected for in the analyses. Should a prospective radiological follow-up study start, we then advocate a more standardized radiographic procedure, for instance with the use of Roentgen stereophotogrammetric analysis (RSA)with fixed marker points in the diaphysis and in the osteochondromas.

Despite the aforementioned limitations this study is the first radiological analysis of longitudinal osteochondroma changes and it showed that parameters length of the femur and height of the osteochondroma could be reliably measured on plain X-rays. However, other measurements such as femoral cross section, the base of the osteochondroma and the distance of the osteochondroma to the joint line of the knee resulted in low reliability.

6. CONCLUSIONS

Length of the femur and height of the osteochondroma can be reliably measured on plain X-rays and both increased over time during growth. No newly formed osteochondromas proximal to the existing osteochondroma were observed during longitudinal growth in this study. It seems likely that the osteochondroma are formed at or near the epiphyses during growth and stay in their place of origin, as the femur grows more distal, realizing a more proximal position of the osteochondroma over time.

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