THE PENNSYLVANIA STATE UNIVERSITY
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RESPONSE OF TRABECULAR BONE AT THE DISTAL FEMUR TO CHANGES IN LOADING WITH THE DEVELOPMENT OF THE BICONDYLAR ANGLE

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ABSTRACT

The femoral bicondylar angle develops during ontogeny in response to changes in loading associated with the onset and maturation of bipedal walking. The magnitude and orientation of loads at the knee joint change significantly during development as the bicondylar angle increases and then stabilizes. The goal of this study is to assess the trabecular bone structural changes of the distal femur in relation to the developing bicondylar angle with the expectation that bone structure will reflect a shift in load magnitude and orientation at the knee during ontogeny. Three-dimensional trabecular bone architecture in the distal femur was quantified from microCT data in 56 individuals from the Norris Farms #36 archaeological skeletal collection. Asymmetry of this trabecular bone architecture between the medial and lateral condyles was quantified by measuring the following morphometric measures: bone volume fraction (BV/TV), degree of anisotropy (DA), trabecular separation (Tb.Sp), trabecular thickness (Tb.Th), and connectivity density (Conn.D). Bicondylar angle was quantified by measuring the angle between the long axis of the bone and the distal femoral metaphyseal and epiphyseal margin. Individuals ranged in age from neonate to adult. We found no significant asymmetry in BV/TV, Conn.D, Tb.Sp, or Conn.D in the metaphysis for all age groups. These results suggest that trabecular bone structure in the distal femoral metaphysis does not reflect changes in load magnitude. However, a trend toward lateral dominance in BV/TV that correlated with the development of the bicondylar was observed, which could be explained by the actions of the lateral collateral ligament.

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Chapter 1

Introduction

The acquisition of a bipedal gait in human juveniles requires the ability to remain balanced on one leg during stance phase (Tardieu & Trinkaus, 1994). The ability to do so is a result of a host of anatomical structures that allow for the alignment of the knee and foot more under the midline to act as a platform for balancing the rest of the body (Tardieu & Trinkaus, 1994). One of these anatomical structures, which develops with the loading of the knee during ontogeny to reduce the moments at the knee, is the bicondylar angle (Shefelbine et. al., 2002). The bicondylar angle is defined as the angle between the diaphyseal axis and a plane that intersects the two most distal points of the femur's metaphysis (Tardieu & Trinkaus, 1994). While the precise mechanisms remain unclear, it has been suggested that the uniquely human bicondylar angle is acquired during development due to faster growth of the medial condyle at the metaphysis of the distal femur (Tardieu & Trinkaus, 1994; Shefelbine et al., 2002). Due to the ontogenetic nature of the bicondylar angle, it is a clear indication of bipedalism in living and extinct hominins (Tardieu & Trinkaus, 1994).

In spite of the significant work on the variation and development of the bicondylar angle, the morphology of the underlying trabecular bone in the distal femur, and how the trabeculae change during growth and in conjunction with the development of the knee joint, has not been widely studied. Studies on the arrangement of trabeculae in the proximal end of the femur have suggested that the trabeculae are aligned along the directions of compressive stresses during loading (Singh et al., 1970). The unique biomechanical loading of the distal femur during development due to the changes in the bicondylar angle provides a natural experiment with which to test the role of mechanical loading in the development of trabecular bone structure.

Long bones grow in width with appositional bone formation, whereby intramembranous ossification results in an increase in diameter (Martin et al., 1998). Endochondral ossification causes growth in length, where hyaline cartilage is replaced by bone as chondrocytes within the original cartilaginous model die (Enlow, 1963). The calcification of this cartilaginous model allows for the incorporation of blood vessels and osteoblasts from the metaphysis, which deposit extracellular matrix to form primary spongy bone in both the diaphysis and epiphysis (Enlow, 1963). According to Wolff's law, bone then has the ability to remodel in response to mechanical loading to form secondary spongy bone during ontogeny. Further studies have explored the correlation between locomotor patterns and loading and the underlying trabecular structure in animals (Barak et al., 2011; Pontzer et al., 2006), and between various primates (Ryan & Walker, 2010; Ryan & Shaw, 2012; Shaw & Ryan, 2012; Ryan & Ketcham, 2005; Fajardo et al., 2007; Griffin, 2008; Skinner et al., 2015; Matarazzo, 2015).

The development of the bicondylar angle in humans during ontogeny has been analyzed as an indicator of a bipedal gait in extant and extinct hominin species (Tardieu & Trinkaus, 1994; Tardieu & Damsin, 1997). Shefelbine et al. (2002) also explored how the bicondylar angle develops with endochondral ossification in response to increased mechanical stress on the medial side of the distal femur, leading to the conclusion that it develops due to changes in skeletal activity as opposed to intrinsic genetic traits (Shefelbine et al., 2002). Ryan and Krovitz (2006) explored this concept in the proximal femur, in which they quantitatively analyzed the 3D structure of the trabecular bone and how it changed during growth. Their findings led to the conclusion that the acquisition of a bipedal gait was apparent in the trabeculae, where increased bone volume fraction and trabecular thickness, as well as a more anisotropic structure resulted from changes in loading patterns (Ryan & Krovitz, 2006).

Gosman (2007) observed changes in trabeculae with the development of the bicondylar angle. His study focused on the proximal tibia, where he found non-significant changes in BV/TV between the lateral and medial proximal tibial volumes of interest. However, the changes in trabeculae showed a biologically significant change at the same time the bicondylar angle developed, indicating a trabecular bone signal with the change in loading (Gosman, 2007). Few studies, however, have directly analyzed the correlation between the bone morphology of the distal femur and the development of the bicondylar angle, which could give important clues on how trabeculae respond to the changing loading demands on the knee. Further, the methods used previously to measure the bicondylar angle were not consistent across age groups, as they employed the use of x-rays and skeletal samples. As a result, those individuals lacking epiphyses had a different set of measures, whereby their bicondylar angle was measured using a metaphyseal plane as opposed to an articular plane, or the sample size was reduced to only juveniles (Tardieu & Trinkaus, 1994; Tardieu et al., 2006; Gosman, 2007). This lack of consistency in measurement across age groups makes the analysis of development difficult and unreliable. A more consistent method would be a standard measurement for all age groups, which would be possible using 3D maximum intensity projections that allow one to see the metaphyseal plane regardless of whether or not the epiphyses were attached.

The objectives of this study are to quantify changes in the trabecular structure of the distal femur and how these changes during growth and development correlate with the bicondylar angle development. Due to the nature of bone remodeling as a result of loading, and the changes in loading on the distal femur with the development of the bicondylar angle, it is hypothesized that changes in the trabeculae will correlate with these variables. In addition, it is hypothesized that there will be significant asymmetry in bone volume fraction between the medial and lateral condyles due to a medial dominant load before the development of the bicondylar angle. But, when the angle fully develops, it is expected that bone volume fraction will become symmetrical between condyles, due to the shift in loading from predominantly medial to neutral.

Chapter 2

Methods

Femoral remains of 56 individuals from the Norris Farms #36 archaeological skeletal collection were used in this study. With burials containing one or more individuals linked to the Oneota cultural tradition of village agriculturalists, the Norris Farms site is a late Prehistoric cemetery dating to approximately 1300 AD from the central Illinois River Valley (Santure et al., 1990). Age-at-death-estimates of the 56 individuals used in this study originated from an earlier analysis of the skeletal collection (Milner et al., 1990). Ages ranged from approximately one month postnatal to adult. For the purposes of this analysis, individuals were assigned to one of five age groups (0-0.9 years; 1-3.9 years; 4-11.9 years; 12-20 years; >20 years), which were based on different levels of locomotor ability and skeletal development. Analysis of the metaphysis was possible across all age groups, while the analysis of the epiphyses was limited to the 4-11.9 age group and older due to the absence of an epiphysis in scans of the younger individuals. Sex differences were not considered in this study because the sex of the juvenile individuals was unknown.

All femora were scanned on the OMNI-X HD-600 microCT scanner (Varian Medical Systems, Licolnshire, IL) at the Center for Quantitative Imaging at the Pennsylvania State University. Each specimen was mounted inside an acrylic tube and was secured using low-density polyethylene foam disks to fix each bone in anatomical position during scanning. All microCT scans were collected using the X-TEK microfocus x-ray source with energy settings of 180 kV and 0.11 mA, 2400 views, two samples per view, and a Feldkamp reconstruction algorithm. Image data were reconstructed as 16-bit TIFF grayscale images with a 1024x1024 pixel grid.

Both metaphyseal and articular bicondylar angles were measured using ortho-projections that were produced using Avizo v.8.0 (Visualization Sciences Group Inc., Burlington, MA, USA). For those individuals without epiphyses, only a metaphyseal bicondylar angle was measured, while those individuals with epiphyses allowed for both measurements. Femora were positioned in Avizo into an anterior view. All bones were transformed to appear as right femora on screen to facilitate standardization of measurements. Landmarks were then placed in the middle of the diaphysis 1/3 and 2/3 of the way along a line extending lengthwise from the bicondylar notch to the top of the femur. The line defined by these two points constituted the diaphyseal axis. Then, the ortho-projection allowed for the placement of landmarks at the two most distal points of the metaphyseal surface even when it had fused with the epiphyses. The line defined by these two points constituted the metaphyseal axis, and the angle created by the intersection of the diaphyseal and metaphyseal axis was measured as the bicondylar angle (Figure 1). A similar procedure was used to measure the articular angle, but the metaphyseal axis was replaced with the epiphyseal axis, which was defined as a line connecting the two most distal points of the epiphyses. Paired t-tests were run for those individuals with both metaphyseal and articular angles to determine if there was a significant difference between the two measurements.

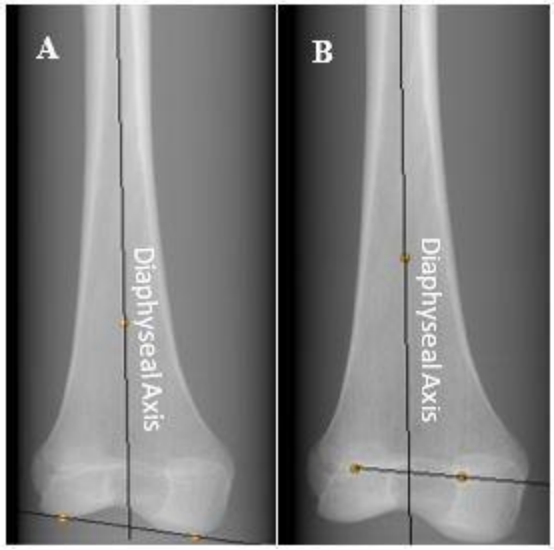

Figure 1. Maximum intensity projections of the distal femur for the same individual with the (A) articular and (B) metaphyseal bicondylar angles defined.

Cubic volumes of interest (VOI) were extracted from both the metaphyses and epiphyses (Figure 2). For the metaphyseal cubes, a region of interest (ROI) was defined using anatomically defined boundaries, with the box extending the width of the distal femur, the lower boundary at the bicondylar notch, and the upper boundary at the approximate area that the condyles began to flare out. For the epiphyseal cubes, an ROI encompassed only the epiphysis, with the box extending the width of the epiphysis, the midpoint aligned with the bicondylar notch, and the height defined by the height of the epiphysis.

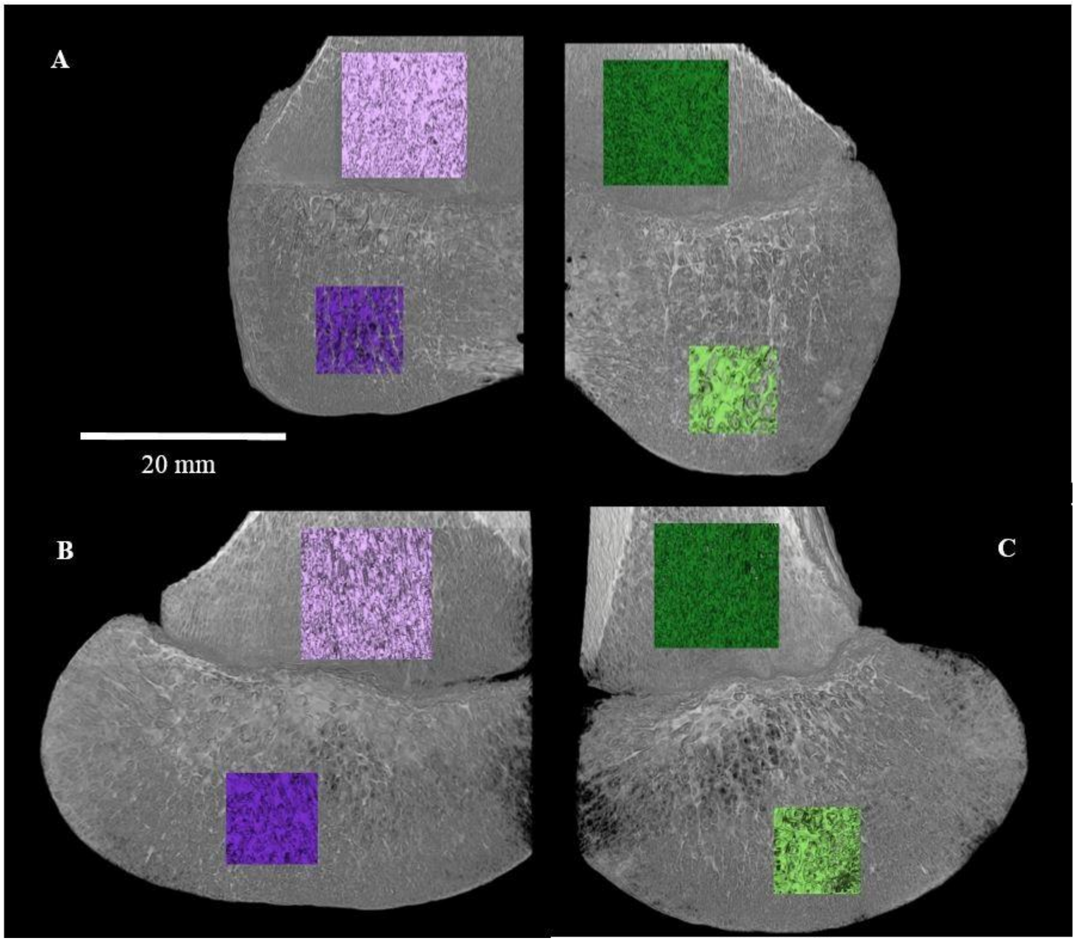

Figure 2. Cubic volumes of interest (VOI) extracted from the distal femur. (A) Anterior view of VOIs displaying metaphyseal and epiphyseal cube placement for the medial (green) and lateral (purple) condyles. Medial views of cubic VOIs in the lateral (B) and medial (C) condyles.

Five morphometric variables for the trabecular bone were quantified for each VOI using the BoneJ plugin for ImageJ (Doube et al., 2010). These included bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), connectivity density (Conn.D), and degree of anisotropy (DA), for which detailed explanations can be found in Shaw and Ryan (2012). Directional asymmetry of metaphyseal and epiphyseal BV/TV and DA was calculated using the formula described by Blackburn (2011):

Directional asymmetry: (Medial-Lateral)/((Medial+Lateral)/2)*100

A positive asymmetry value indicates medial dominance, while a negative asymmetry value indicates lateral dominance. Calculating asymmetry not only serves as an indicator of differences in the trabeculae between condyles, but also as a way of controlling for the variability between individuals within a population. By calculating asymmetry, variability within a population will not affect findings as asymmetry pairs the measures for each individual for a constant variable.

It was then determined whether or not the calculated asymmetry values were significantly different from zero. Non-parametric tests were run due to the non-normal distribution of the asymmetry values. Wilcoxon-signed rank tests were performed for the asymmetry of the five morphometric variables measured in order to determine if the median values for each age group were significantly different from zero. Two-tailed Wilcoxon-signed rank tests were performed for the metaphysis and epiphysis, with the null hypothesis being asymmetry equal to zero and the alternative hypothesis being not equal to zero.

Chapter 3

Results

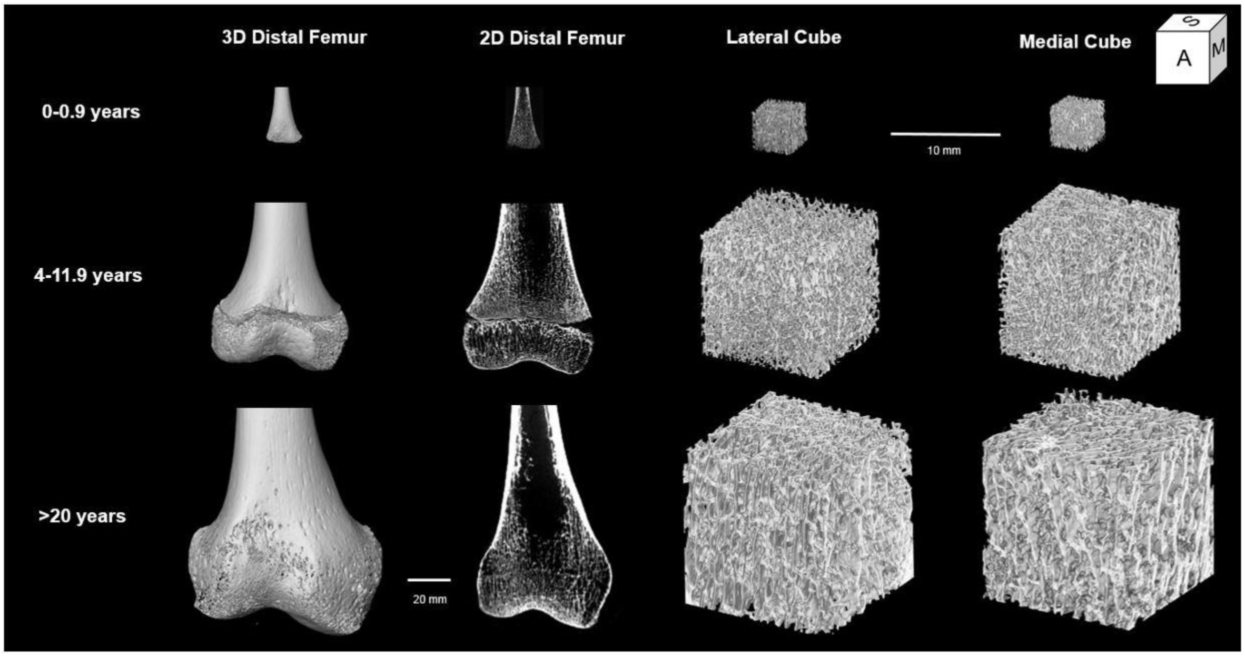

Figure 3. Age groups 0-0.9, 4-11.9, and >20 represented down the rows, respectively, with 3D and 2D scans of the distal femur for a representative individual from the designated age group. Lateral and medial cubes of trabeculae represent the VOIs extracted for quantifying morphometric measures.

The results and visualization of the microCT scans of the distal femurs can be seen in Figure 3 above. The 3D image and its corresponding 2D image display the underlying trabeculae of the distal femur, as well as the clear differences in size between age groups. The lateral and medial cubes display the resulting volumes of interest that were used for analyzing the indicated morphometric measures, oriented according to the reference cube. These VOIs also display the clear differences in size between age groups.

Metaphyseal and Articular Bicondylar Angles

Table 1. Metaphyseal and Articular Bicondylar Angles, mean angles for each age groups and the resulting p-value of a paired t-test between metaphyseal and articular angles.

Age Group	Metaphyseal	Articular	P-value
0-0.9 years	1.96		
1-3.9 years	4.40		
4-11.9 years	5.71	10.78	<0.01
12-20 years	5.23	9.39	<0.001
>20 years	7.14	10.48	<0.001

As indicated by the results of the paired T-tests between metaphyseal and articular angles, the two bicondylar angles were significantly different with the articular angle greater in all cases ($p<0.01$, $p<0.001$, $p<0.001$ respectively for each age group). In addition, these mean angles are similar to those found in previous studies performed on both metaphyseal and articular bicondylar angles (Tardieu & Trinkaus, 1994).

Bone Volume Fraction Asymmetry

Table 2. Wilcoxon Signed Rank Test, median and resulting p-values to determine if the median BV/TV asymmetry values were significantly different from zero.

Age Group	Metaphyseal		Epiphyseal	
	Median	P-Value	Median	P-Value
0-0.9 years	3.47	0.26		
1-3.9 years	-1.84	0.89		
4-11.9 years	-8.74	0.23	-23.79	0.18
12-20 years	-1.18	0.91	-22.25	0.08
>20 years	-1.00	0.80	-12.54	0.03

Across all age groups in the metaphysis, the results of the Wilcoxon-signed rank tests indicate that BV/TV is symmetrical with respect to the medial and lateral condyles. In the epiphysis, however, BV/TV appears higher on the lateral side for all age groups, but only significantly so in the >20 age group (p<0.05).

Degree of Anisotropy Asymmetry

Table 3. Wilcoxon Signed Rank Test, median and resulting p-values to determine if the median DA asymmetry values were significantly different from zero.

Age Group	**Metaphyseal**		**Epiphyseal**	
	Median	**P-Value**	**Median**	**P-Value**
0-0.9 years	-1.75	0.45		
1-3.9 years	-13.79	0.01		
4-11.9 years	-1.41	0.73	-3.93	0.79
12-20 years	-16.11	0.01	12.60	0.23
>20 years	-16.13	0.02	11.52	0.09

In the metaphysis, DA showed large variability across age groups. The results indicate a switch from symmetrical DA in the 0-0.9 age group to higher DA on the lateral side in the 1-3.9 age group (p<0.01). However, the 4-11.9 age group showed symmetrical DA, followed by higher DA on the lateral side once again in the 12-20 and >20 age groups (p<0.01, p<0.05). Anisotropy was symmetrical across all age groups in the epiphysis.

Trabecular Thickness Asymmetry

Table 4. Wilcoxon Signed Rank Test, median and resulting p-values to determine if the Tb.Th asymmetry values were significantly different from zero.

Age Group	Metaphyseal		Epiphyseal	
	Median	**P-Value**	**Median**	**P-Value**
0-0.9 years	13.42	0.03		
1-3.9 years	7.33	0.07		
4-11.9 years	2.56	0.62	2.58	0.79
12-20 years	13.41	0.02	2.56	0.55
>20 years	5.29	0.04	10.41	<0.01

Similar to DA, Tb.Th showed extensive variability in the metaphysis with medial dominance in the 0-0.9, 12-20 and >20 age groups ($p<0.05$), but symmetrical Tb.Th in the 1-3.9 and 4-11.9 age groups. Similar to DA, the epiphysis showed significance in the >20 age group with medial dominant Tb.Th ($p<0.01$), but was unremarkable otherwise.

Trabecular Separation Asymmetry

Table 5. Wilcoxon Signed Rank Test, median and resulting p-values to determine if the median Tb.Sp asymmetry values were significantly different from zero.

Age Group	Metaphyseal		Epiphyseal	
	Median	**P-Value**	**Median**	**P-Value**
0-0.9 years	0.80	0.90		
1-3.9 years	3.18	0.62		
4-11.9 years	17.33	0.29	19.84	0.11
12-20 years	5.50	0.64	21.84	0.02
>20 years	6.80	0.21	26.28	<0.01

Similar to the results of BV/TV, the findings of the Wilcoxon-signed rank tests indicate symmetrical Tb.Sp in the metaphysis across all age group. However, in the epiphysis, the 12-20 and >20 age groups showed significantly medial dominant Tb.Sp ($p<0.05$, $p<0.01$), but was symmetrical in the 4-11.9 age group.

Connectivity Density Asymmetry

Table 6. Wilcoxon Signed Rank Test, median and resulting p-values to determine if the median Conn.D asymmetry values were significantly different from zero.

Age Group	Metaphyseal		Epiphyseal	
	Median	**P-Value**	**Median**	**P-Value**
0-0.9 years	-5.38	0.57		
1-3.9 years	5.44	0.50		
4-11.9 years	13.59	0.83	-48.09	0.11
12-20 years	2.19	0.55	-39.95	0.01
>20 years	6.92	0.66	-58.33	<0.01

Conn.D was unremarkable in the metaphysis like BV/TV and Tb.Sp. In the epiphysis, the 4-11.9 age group's median indicates lateral dominance, but only the 12-20 and >20 age groups were significantly lateral dominant ($p<0.05$, $p<0.01$).

<u>BV/TV Asymmetry vs. Bicondylar Angle</u>

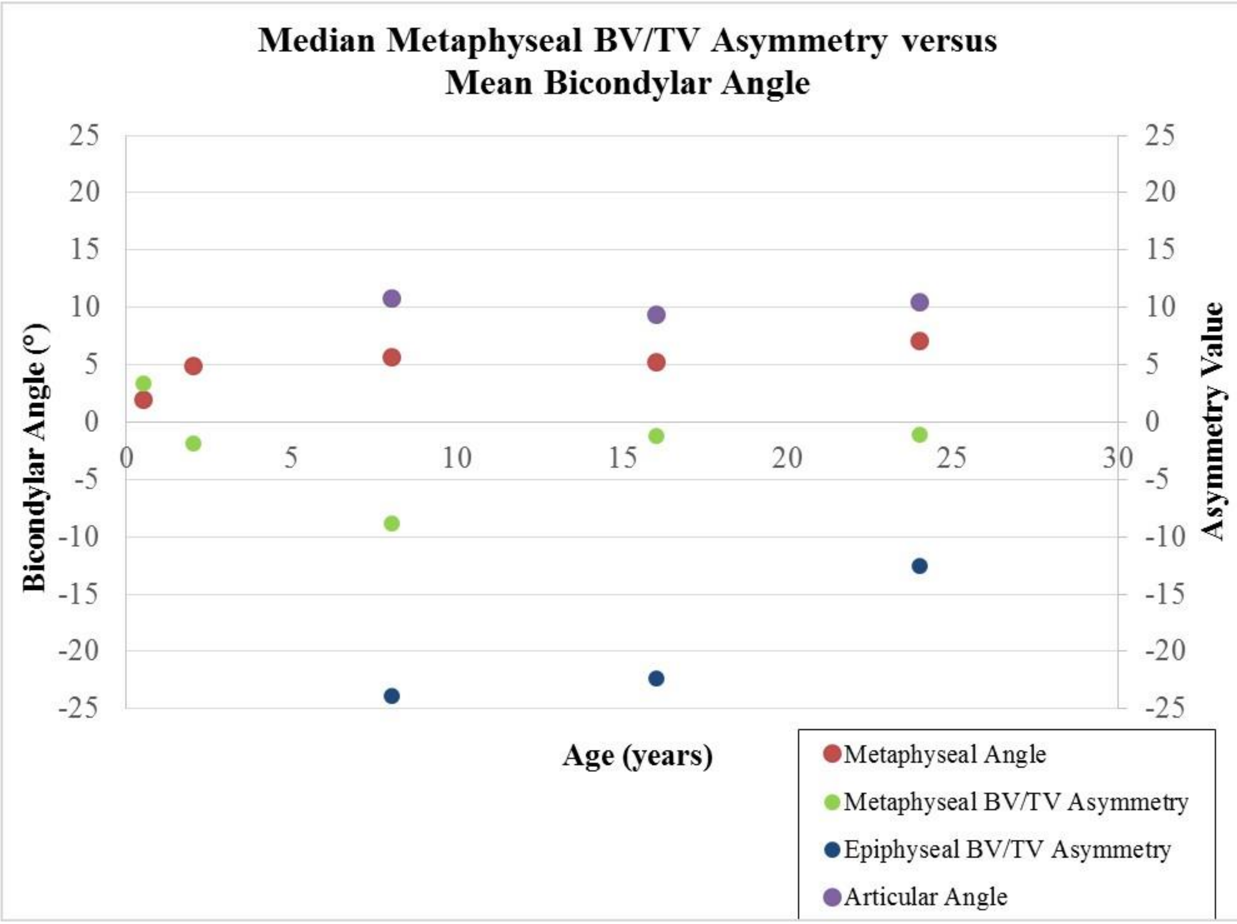

Figure 4. Median metaphyseal and epiphyseal BV/TV asymmetry values versus the five designated age groups graphed against the mean metaphyseal and articular bicondylar angle values versus the designated age groups.

Figure 4 above displays the relationship between BV/TV and the development of the metaphyseal bicondylar angle. As seen in the figure, as the metaphyseal angle develops across the age groups, BV/TV asymmetry switches from a positive value, indicating medial dominance, to a negative value, indicating lateral dominance. However, despite these values, the results of Wilcoxon-signed rank tests indicated symmetry across all age groups for BV/TV in the metaphysis. Still, these findings could be biologically significant even though they are not statistically significant. In the epiphysis, a similar trend may exist, but a lack of individuals in the first two age groups prevents the observation of it. However, lateral dominance in BV/TV with a trend toward symmetry in the older age groups may also be present in the epiphysis. Along with this, there are clear differences between the values of asymmetry in the metaphysis versus epiphysis, as indicated by the large gap between asymmetry values in this figure.

Chapter 4

Discussion

The findings of this study establish a significant difference between the metaphyseal and articular bicondylar angles. This is important to consider when conducting further studies on the bicondylar angle and its changes during ontogeny or comparisons between individuals and other studies, where articular and metaphyseal angles will be different between the same individual. In addition, the use of maximum intensity projections proved effective for measuring an articular and metaphyseal bicondylar angle on individuals whose growth plate had fused, making it impossible to measure a metaphyseal angle on the physical bone. Our results for both angles are assumed to be reliable due to their similarity to other studies that measured both the metaphyseal and articular angles (Tardieu & Trinkaus, 1994). This study, however, has opened up the range of specimens that can have both angles measured.

Prior to the walking phase in human development, the lack of a bicondylar angle causes the alignment of the knee to appear more varus than an adult stance, which is described as more valgus, and this has been found to result in a predominantly medially-positioned load (Tardieu & Damsin, 1997; Shefelbine et al., 2002). However, as the individual grows and the angle develops, a more neutral stance results in a more neutral load of the condyles (Johnson et al. 1980). The hypothesis and expectation for this study was a correlation between the shift in loading pattern as a result of the bicondylar angle and changes in the trabeculae. Effectively, this study aimed to find a signal in the trabeculae during development in the distal femur. Given that changes in bone volume fraction have been established as a signal of loading due to the high correlation between bone volume fraction and elastic properties (Hodgskinson & Currey, 1990a; Hodgskinson & Currey, 1990b; Mittra et al., 2005), a significant correlation between bone volume fraction and bicondylar angle was expected in concert with the shift in loading during the development of bipedal gait in humans (Ryan & Walker, 2010; Gosman, 2007). However, our findings contradict this expectation, as there was no correlation between BV/TV and bicondylar angle in either the metaphysis or epiphysis.

With bone volume fraction responding to loading, the asymmetrical loading of the femoral condyles when a human begins walking is expected to be reflected in significant differences in bone volume fraction between the medial and lateral condyles. In theory, if alignment starts as more varus, greater loading of the medial condyle would result in a significantly higher BV/TV, and as the bicondylar angle developed, this difference would cease to be significant as the angle results in a more neutral and even loading of the condyles. Since Wilcoxon signed rank tests determined that, throughout all age groups, the median BV/TV asymmetry values between the medial and lateral condyles in the metaphyses were not significantly different from zero, this expectation has been refuted. With no significant differences in BV/TV asymmetry in all age groups in the metaphysis, the results suggest that there is no response to the changes in loading as a result of the development of the bicondylar angle in the metaphysis.

However, there may be a biologically significant pattern in bone volume fraction similar to the results Gosman (2007) obtained, with a switch from medial dominance prior to walking to lateral dominance in individuals with a bicondylar angle, ending with an almost symmetrical ratio. This would suggest as Gosman (2007) did, that there may be some kind of balance adjustment post-puberty. This can be seen in Figure 4 above. This switch in asymmetry in bone volume fraction can be seen with the medians of each age group. A positive value indicates medial dominance, which is seen in the 0-0.9 age group, where a varus stance is expected.

However, as walking becomes the main form of locomotion in the 1-3.9 age group and heavy medial loading results in a bicondylar angle and more valgus stance, a negative asymmetry suggests a switch in dominance from medial to lateral. The timing of this event also agrees with the observations of Gosman (2007) in the proximal tibia.

An explanation for this lateral dominance during the 1-3.9 age group could come from other stabilizing structures within the knee. During the development and the acquisition of a bipedal gait, which is taking place in this age group, medial dominance is expected until the angle has fully developed, and potentially into an adult gait (Morrison, 1970; Harrington, 1976). The biomechanics of this juvenile stance may explain the switch to lateral dominance in BV/TV. As the medial side bears the majority of the load with walking and articulation with the tibia, the lateral condyle of the distal femur may experience a lift off of the proximal tibia due to an external adduction moment (Schipplein & Andriacchi, 1991). To counteract this, and keep the distal femur in place, studies have found that the lateral collateral ligament acts as a stabilizer that resists this external adduction (Grood et al., 1988; Markolf et al., 1976; Veltri et al., 1995; Wroble et al., 1993). In doing so, it is assumed that the insertion point of this lateral collateral ligament on the lateral side of the distal femur would add strain to the lateral condyle, at which point the lateral condyle would respond with an increase in BV/TV.

In the epiphysis, with significantly higher lateral BV/TV in the >20 age groups, there could be a delayed signal to the change in loading with the development of the bicondylar angle, as both the metaphyseal and articular angles stabilized in the 4-11.9 age group. Since epiphyses are only available for individuals >8 years of age, at which point both the metaphyseal and articular bicondylar angles appear to stabilize, the trabecular bone should already be a product of the changes in loading as a result of this angle.

In addition to these reasons, the lack of a clear signal of the changes in loading in the distal femur with the development of the bicondylar angle could be due to a failure in taking anatomically symmetric VOIs. In other words, although the VOIs were placed in line with one another in each condyle, it is possible that the distal femur does not articulate in a way that sets these VOIs in the same trajectory of forces during articulation. As a result, the story told by the morphometric measures found in each condyle do not accurately represent the response to loading. In fact, it is likely that the lateral condyle articulates and experiences more loading toward its posterior side relative to the medial condyle during locomotion as the lateral center of contact of this condyle during flexion moves posterior due to the internal rotation of the tibia (Draganich et al., 1984; Kettelkkamp & Nasca, 1973; Sledge & Walker, 1984). This is supported by the finding that the lateral condyle's maximal strength is located posteriorly, while the medial condyle's is located more centrally (Hvid & Hansen, 1985). Extracting VOIs that take into account these anatomical differences in articulation may result in a more accurate picture of how the trabeculae responds to changes in loading.

As seen in Figure 4, there are differences in the trend between the metaphyseal and epiphyseal bone volume fraction with development. While the metaphyseal bone volume becomes symmetrical with development, the epiphyseal bone volume stays mostly lateral dominant. There is also a clear difference in the asymmetry values between the metaphysis and epiphysis, with much greater lateral dominance in the epiphysis. Further work to examine the differences in the morphology of the trabeculae between the metaphysis and epiphysis could reveal information on how differences in the mode of bone growth affect trabecular structure. In particular, if growth and orientation relative to the growth plate in the metaphysis results in differences in trabecular structure compared to radial growth in the epiphysis, as well as the effect of different loading schemes between the metaphysis and epiphysis (Frost & Jee, 1994).

There is extensive variability of anisotropy asymmetry in the metaphysis. A lack of asymmetry in anisotropy is expected for infants (0-0.9 age group) due to their relatively small amount of time on two legs. Higher degrees of anisotropy in the 1-3.9 age group suggests that the lateral condyle in the metaphysis has more regular loading, which is a significant finding, but somewhat difficult to interpret as the 4-11.9 age group is once again symmetrical. It is possible, however, that this is due to the small sample size of this age group (8 individuals) or something unique to this age group within this specific population. Higher anisotropy is once again acquired in the 12-20 and >20 age groups, which indicates that once again, there is more regular loading of the lateral condyle in the metaphysis. However, in the epiphysis in the >20 age group, the opposite is found with a significantly higher anisotropy in the medial condyle. The location of the metaphysis and epiphysis with relation to loads may be important to consider when interpreting these findings. It may be that the metaphysis is orienting its trabeculae relative to the growth plate, while the epiphysis is orienting its trabeculae relative to the force it experiences as it articulates with the tibia. If that were the case, however, the orientation relative to the growth plate would most likely result in symmetrical degrees of anisotropy across condyles in the metaphysis, which was not found.

Similar to bone volume fraction, both trabecular separation and connectivity density were symmetrical in the metaphysis across all age groups. This is somewhat expected, as a trend or signal in these two morphometric measures would be surprising given the lack of a signal in the metaphysis from bone volume fraction. It is important to note, however, that trabecular separation and connectivity density showed opposite trends in the epiphysis, as trabecular separation became medial dominant while connectivity density became higher on the lateral side. Still, significant asymmetry in the two older age groups is similar to the findings with bone volume fraction, so it is doubtful that a signal will be seen in these morphometric measures if it is not seen with bone volume fraction. Trabecular thickness, on the other hand, showed trends more similar to anisotropy, with extensive variation in the metaphysis. However, while anisotropy was always higher on the lateral side, trabecular thickness showed medial dominance. Significantly medial dominant trabecular thickness in the >20 age group is expected given the significantly lateral dominant connectivity density, as these two measures typically correlate with one another.

These findings on morphometric measures indicate the importance of further research on this topic. In particular, an analysis of the 3D orientation of the trabeculae with relation to the development of the bicondylar angle and the metaphysis could produce findings on a correlation between the two variables. However, it is possible that a signal of locomotor changes will not be present in the trabeculae. Similar to the findings that the lateral collateral ligament acts as a major stabilizer during locomotion, Shelburne et al. (2006) found a host of stabilizer muscles and ligaments in the knee are acting during normal walking on the lateral side synergistically with the medial dominant load, which may prevent a signal. Given that adolescence and even adulthood is not limited to simple walking, it is possible that dynamic movements throughout life are more impactful on the morphology of bone, so the locomotor changes occurring during development are not significant enough to affect trabecular structure. As a result, further studies that take into account the dynamic forces at the distal femur for a more precise and detailed characterization of trabecular structure are necessary.

Several other factors should be considered when conducting further research on this topic. First, it is possible that endochondral ossification is highly patterned. As a result, trabecular structure is the product of a predetermined blueprint as opposed to a self-guided response based on the magnitudes and orientation of external loads (Lovejoy et al., 2003). Second, the proximal tibia may hold important information, and studies that account for both the proximal tibia and the distal femur in the knee joint may reveal important information on the forces experienced by the two with articulation during a variety of movements. Finally, a signal within the trabeculae may not be apparent unless a suite of morphometric measures are considered at the same time, as opposed to individually, similar to what Ryan and Shaw (2012) found.

Chapter 5

Conclusion

This study analyzed and quantified changes in the trabecular structure in the distal femur with development of the bicondylar angle to determine if these changes correlated with the shift in loading. In addition, this study developed a method for measuring metaphyseal and articular bicondylar angles in individuals with fused growth plates. The findings of the present study indicate that a signal in the trabeculae of changes in loading is not clear, and given the statistical results, our null hypothesis cannot be rejected. However, a trend was found, suggesting that loading switches from medial to lateral dominant, followed by more symmetrical loads in mature adults. This lateral dominance can potentially be explained by the role of the lateral collateral ligament in stabilizing the knee joint during development. Further work that takes into consideration other variables associated with the complex knee joint may be able to more clearly identify a signal in the trabeculae.

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ACADEMIC VITA

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EDUCATION

The Pennsylvania State University, University Park, PA Fall 2011 – Present

- Schreyer Honors College
- Bachelor of Science in Biological Science with Health Professions Option
- Undergraduate Advisor: Dr. Ronald Markle
- Expected Graduation: May 2015

RESEARCH EXPERIENCE

Undergraduate Research Fall 2013 – Present

- Work in Dr. Tim Ryan's paleoanthropology lab
- Researching changes in bone morphology with development
- Focus on femur and the development of the bicondylar angle
- Plans to complete an undergraduate honors thesis

TEACHING EXPERIENCE

Undergraduate Assistant-Teaching Assistant Spring 2013

- Assistant to the TA, helping run the laboratory portion of biology classes
- Answer students' questions and help to prep lab room

Undergraduate Teaching Assistant Fall 2013 – Present

- Run laboratory portion of Introductory Biology course
- Teach students necessary concepts and lead them through the labs
- Responsible for laboratory grades, answering students' questions, and improving their laboratory skills
- Work closely with Biology course coordinators and graduate students
- Requires extensive knowledge of fundamental biological concepts in order to teach

Student-Athlete Tutor, Morgan Center, University Park, PA Fall 2014 – Present

- Tutor Penn State student-athletes in a variety of subjects, including introductory chemistry and biology
- Responsible for improving the student-athlete's understanding of the material, as well as acting as an academic role model
- Demands a good understanding of the material
- Requires effective communication and the ability to relate to the tutee
- Involves helping the student-athlete to develop good study skills and habits related to the course material

HONORS AND AWARDS

- **Enrolled in Penn State University Schreyer Honors College** (2011 – Present)
- **Schreyer Honors College Academic Excellence Scholarship** (2011 – Present)
- **Dean's List** (7/7 semesters)
- **New York Times Civic Engagement Public Speaking contest nominee** (Fall 2012)
- **U.S. Lacrosse High School Academic All-American** (2011)
- **Presidential Service Award** (Fall 2010)

TECHNICAL SKILLS

- EMT-B certified with EVOC and HazMat-Operations certifications
- Basic laboratory procedures and skills
- Experience in patient contact and medical documentation

ACTIVITIES AND AFFILIATIONS

Volunteer EMT-B, Centre LifeLink, State College, PA 2012 – August 2013

- Responded to emergency medical situations and provided patient care on scene
- Was responsible for well-being of patient and making decisions in a short amount of time using critical thinking
- Transported to hospital and stabilized patient en-route
- Documented thoroughly all that happened during the call in a Patient Care Report
- Worked closely with Paramedics and Emergency Department staff
- Over 400 volunteer hours and 100 calls

Participant of Penn State Hershey Medical Group Career Observation Spring 2014

- Shadowed a variety of medical specialties, from family physician to dermatologist
- Had extensive one-on-one time with doctors
- Allowed for observation of doctors while they interacted with patients

Physical Therapy Intern, Cardin & Miller, Mechanicsburg, PA 2012-May 2014

- Worked closely with physical therapists and physical therapist assistants
- Was responsible for leading patients through exercises and stretches
- Was responsible for keeping the clinic in order and making sure patients were comfortable

Penn State Global Medical Brigades Member 2011 – May 2012

- Worked volunteer hours to raise funds for a medical brigade abroad
- Volunteered on a medical brigade to rural villages in Panama (Spring Break 2012)
- Part of a team that set up medical clinics in underserved areas of Panama, which provided medical, dental, and pharmaceutical care
- Taught the locals preventative healthcare for sustained improvement