Age-Related Sexual Dimorphism of the Proximal Femur in Portuguese Water Dogs: Implications for Total Hip Replacement and Osteoporosis

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DISCLOSURE: The authors have nothing to disclose

INTRODUCTION: After menopause the femora of human females undergo a disproportionate rate of endosteal resorption when compared to subperiosteal bone apposition, resulting in increased bone fragility and potentially impaired longevity of femoral endoprostheses in total hip replacements (THRs) [1]. This modeling pattern, which is not observed in males, can result in poor osseointegration of press-fit components potentially increasing the likelihood of THR failure [**2**]. Press-fit femoral component subsidence is associated with canal flare index (CFI) in both canines and humans (see **Fig.1**; CFI = X/Y) [2, **3**]. Canines with components implanted into femora with CFI <1.8 were found to be six times more likely to subside than those with CFIs of 1.8-2.5, and 72 times more likely to subside than implants in femora with CFI ≥2.5 [2]. During the aging process the human femur exhibits decreases in CFI in both sexes, which is attributed to the disproportionate expansion of the lateral medullary canal and decreased lateral cortex — as reflected by a similar decrease in the lateral canal flare index (LFI) [3]. Interestingly, a decline in the cortical index (CI) was observed in the females only (indicates a reduction in cortical thickness) [3]. The canine femur could be a useful model for investigating details of genetic factors that might mediate these sex-related differences in humans. Studies in canine femora indicate a weak negative relationship between age and CFI [2, 4]. We analyzed a large sample (n=342) of Portuguese water dog (PWD) femora to test the hypothesis that this breed undergoes age-related sexual dimorphisms similar to humans. Detecting sexual dimorphisms of the PWD femur and their correlations with aging can help develop age- and/or sex-specific femoral THR components for this breed. Additionally, these canine studies can elucidate genetic factors that influence the emergence of these age-related morphologies in both species, which has implications for advancing understanding of the emergence of fragility of the human femur.

METHODS: With IACUC approval, PWD carcasses were autopsied for various organ pathologies in prior studies that were part of a large research effort known as the Georgie Project [5, 6]. Measurements for total femoral length (L.Tot) were done on n=342 femora (M=143, F=199) using digital calipers (Mitutoyo). The femora were then radiographed in a standardized anterior-posterior projection and digitized. Radiographs were analyzed using ImageJ (https://imagej.nih.gov/ij/) to measure various parameters including the canal flare index (CFI), which is the ratio between proximal and distal medullary diameters (Prox.MD / Dist.MD; X/Y in **Fig. 1**). Prox.MD was measured at the apex of the lesser trochanter, and Dist.MD was measured at the isthmus. A perpendicular vertical line was placed at the midpoint of the Dist.MD dividing the femur into two portions to calculate the lateral flare index (LFI) and medial flare index (MFI) (similar to [3]). The LFI is calculated by dividing the lateral ½ of the Prox.MD by the lateral ½ of the Dist.MD, and the MFI is calculated by using the respective medial measurements. Total medullary area (T.MA) was calculated as the sum of the areas for the 4 quadrants of the femur as depicted in Figure 1 (A,B,C, and D). Additional measurements included cortical thickness and the cortical index at the X (proximal) and Y (distal) locations of **figure 1** and at ½ the vertical distance between these locations (middle). Cortical index is determined from transverse outer and inner (medullary) diameters: (outer – inner)/(outer). Statistical analyses included a robust linear regression analysis. All statistics were estimated using custom scripts in R(1) (http://www.R-project.org/). Pearson corr. coefficients were estimated using the 'cor' function, robust line fitting was with the 'rlm' function.

RESULTS: Correlations of canal flare indices (CFI, MFI, LFI) vs. age, when significant, were typically weaker ($r < 0.2$) than reported in humans [3], including: total sample (CFI, p=0.08, r= -0.10), males only (CFI, p=0.6, r= -0.05), and females only (CFI, p=0.08, r= -0.12) (**Fig. 2**, blue = males). Correlations of LFI and MFI vs. age of the total sample are (p=0.06, r= -0.1) and (p=0.3, r= -0.05) respectively, showing an overall weak negative trend with LFI (resembling human patterns, but weaker relationships in canines). Male femora showed no significant decline in the cortical indices, while the female femora showed a significant decrease in Dist.CI vs. age (p=0.04, r= -0.14), which corresponds to the significant age-related decreases in Dist.CT of both the medial (p=0.03, r= -0.15) and lateral cortices (p<0.01, r= -0.20). The female femora showed no significant change in the Prox.CI (p=0.7) and a trend in Mid.CI (p=0.06, r= -0.13). The T.MA showed a significant, but weak, relationship with age in males (p=0.04, r= 0.17) and no relationship in females. When the T.MA was normalized for the length of the femur the entire sample showed an overall weak positive trend (p=0.06, r= 0.10), while again only the male femora showed a significant relationship (p=0.03, r= 0.17).

DISCUSSION: We performed this study in see if age-related patterns in the canine femur model resemble those known to occur in the human proximal femur [3]. If this was the case, then perhaps similar genetic factors influence the emergence of these morphologies in both species [7]. Our PWD data showed a weak overall negative tendency of age vs. CFI for the entire sample (p=0.08, r= -0.10). While not statistically significant, this age-related tendency was most influenced by the female sex (p=0.08, r= -0.12), and a decrease in LFI approaching significance as well (p= 0.06, r= -0.10). This result reflects the fact that only the female PWD showed a significant age-related decrease in the distal cortical index (Dist.CI) (p=0.04, r= -0.14). While the PWD femur does not exhibit age-related changes to the same extent observed in humans, modeling patterns of both species have some important similarities. Hence, a subset of our data has potential translational value for understanding aging of the proximal human femur, suggesting that genetic influences found to be important in PWD femora might also apply to humans. Our ongoing inquiry into potential genetics factors may therefore help better understand age-related femoral dimensional morphology changes that correlate with the longevity of intramedullary prostheses and also with respect to the reduction of cortical vs. cancellous bone mass seen with aging in humans.

SIGNIFICANCE/RELEVANCE: Age-related changes in the regional proportions of the cortex and medullary portions of the femur have significant implications when planning for THRs using press-fit components, where maximal contact between the prostheses and cortical bone is desirable for osseointegration. Cortical thinning and medullary expansion in the proximal femur also contribute to fragility of this area.

REFERENCES: [1] Ruff and Hayes (1988) J Orthop Res 6:886-; [2] Rashmir-Raven et al. (1992) Vet Surg 21:327-; [3] Casper et al. (2012) J Orthop Res 30:1162-; [4] Ganz et al. (2010) Vet Surg 39:688-; [5] Chase et al. (2002) PNAS 99:9930-; [6] Chase et al. (2005) Am J Med Genet A.135:334-; [7] Ostrander and Wayne (2005) Genome Research 15: 1706-.