



Assessment of the bilateral asymmetry of human femurs based on physical, densitometric, and structural rigidity characteristics

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ABSTRACT

The purpose of this study was to perform a comprehensive geometric, densitometric, biomechanical, and statistical analysis of paired femurs for an adult population over a wide age range using three imaging modalities to quantify the departure from symmetry in size, bone mineral density, and cross-sectional structural rigidities.

Femur measurements were obtained from 20 pairs of cadaveric femurs. Dimensions of these anatomic sites were measured using calipers directly on the bone and plain radiographs. Dual energy X-ray absorptiometry was used to measure bone mineral density. Bone mineral content and axial and bending rigidities were determined from the CT imaging.

No differences were observed between the geometric measurements, DXA based bone mineral density and axial and bending rigidities of left and right femurs ($P > 0.05$ for all cases). Left and right proximal femurs are not significantly different based on geometric, densitometric, and structural rigidity measurements. However, absolute left–right differences for individual patients can be substantial. When using the contralateral femur as a control, the number of femur pairs required to assess significant changes in anatomic dimensions and structural properties induced by a tumor, infection, fracture, or implanted device can range from 3 to 165 pairs depending on the desired effect size or sensitivity (5% or 10% difference).

This information is important both for femoral arthroplasty implant design and the use of the contralateral femur as an intra-subject control for clinical assessment and research studies. In addition, our statistical analysis provides sample size estimates for planning future orthopedic research studies.

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1. Introduction

Bilateral symmetry is often assumed in clinical assessments. The contralateral limb is frequently used as an intra-subject control in research studies that assess changes in bone size, shape, density, and structural properties as a result of tumor, infection, fracture, asymmetric loading applications, or device implantation in one of the bones forming the pair. The gold standard of practice for measuring areal bone mineral density (BMD), osteoporosis screening, and fracture risk analysis is dual energy X-ray absorptiometry (DXA), which scans a single hip for average BMD and bone mineral content (BMC) values (Adachi, 1996; Cody et al., 1996; Khunkitti et al., 2000; Bainbridge et al., 2004). Particularly relevant to the femur is the use of the contralateral

femur as a template for robot controlled milling of the proximal femur in computer assisted total hip arthroplasty and computer assisted navigation, and preoperative planning systems (Bargar et al., 1998; DiGioia et al., 1998; Noble et al., 2003; Gonzalez Della Valle et al., 2005).

There are relatively few studies that have comprehensively analyzed the symmetry of femur pairs with respect to anatomic dimensions, bone density, and geometric structural properties. The majority of previous investigations have focused primarily on the laterality differences in bone geometry and density as a function of subject activity during sports or work. The variation in bilateral symmetry was demonstrated to be considerable in the humeral shaft of tennis players (Haapasalo et al., 1998), where the BMD and BMC of the dominant hand increased by 25% and 29%, respectively (Kannus et al., 1994). Similar results were found for the dominant femur of female soccer players (Alfredson et al., 1996). Additional studies have shown a correlation between BMD and BMC and right or left handedness (Yang et al., 1997; Gumustekin et al., 2004; Plochocki, 2004; Vrahori et al., 2004). Geometric bilateral asymmetry is well documented. Evaluation of

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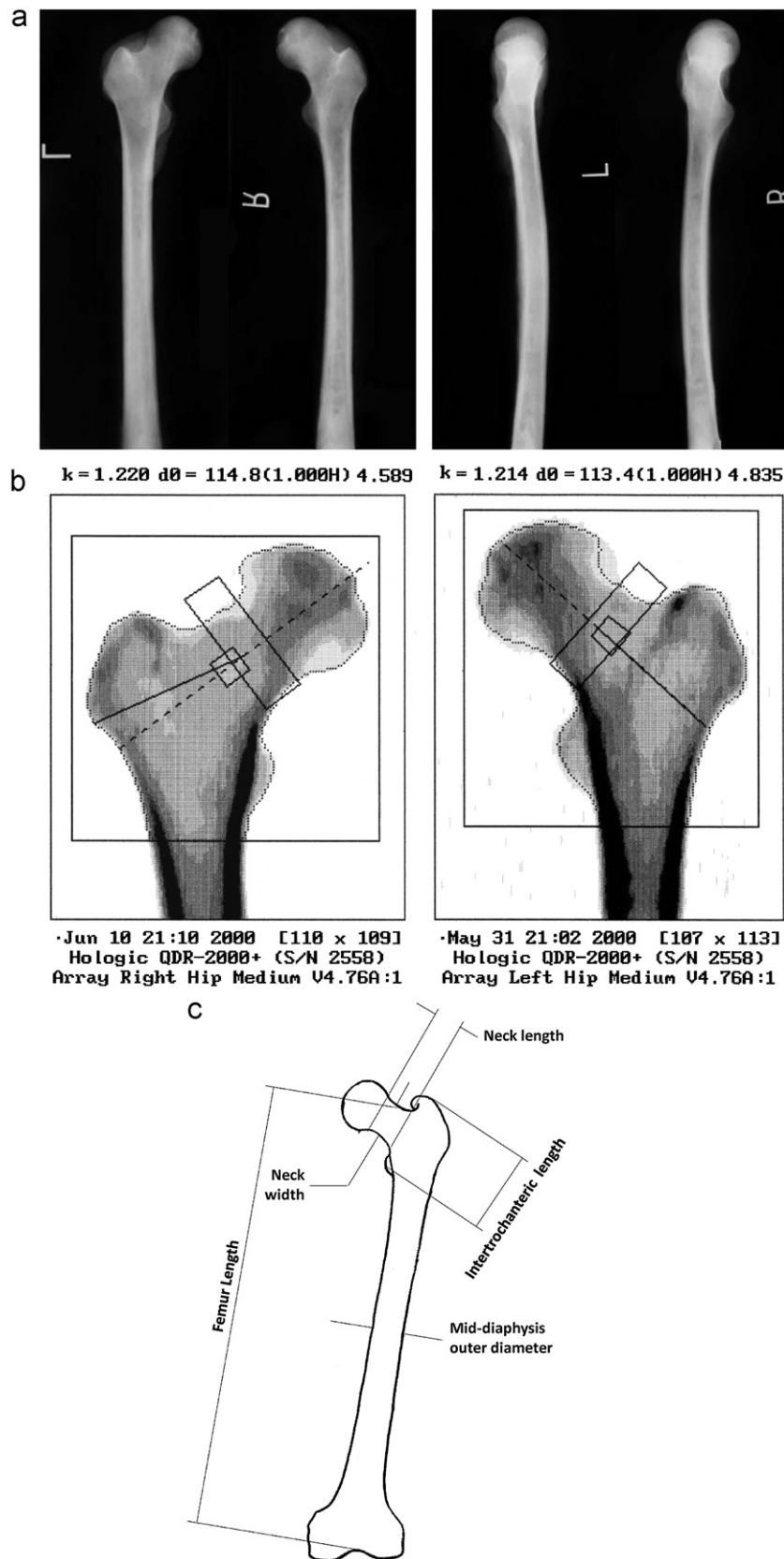


Fig. 1. Representative anterior–posterior and lateral plain film radiographs (a) and DXA scan (b) from the study. Representation of the anthropomorphic measures obtained directly from plain film radiographs.

178 matched femurs from skeletally mature cadavers demonstrated that femoral length differed by 1.2 cm at the 99th percentile (Strecker et al., 1997). Asymmetry of bone morphology at other skeletal sites including the wrist, forearm, pelvis, and long bones has also been well documented using different imaging modalities (Hiramoto, 1993; Freedman et al., 1998; Gualdi-Russo, 1998; Livshits et al., 1998).

However, variations in cross-sectional geometric properties such as the area and moment of inertia, cross-sectional structural properties including axial and bending rigidity measurements, and anthropometric details specific to anatomic femoral hardware design remain unknown. These properties are relevant to the determination of the load capacity of the femur for a wide age range of mostly male adults.

A statistical analysis was performed to provide percent difference between right and left matched femoral pairs for anatomical, geometrical, structural, biomechanical, and densitometric measurements. Additionally, sample size requirements for 80% power were given for detecting 5% and 10% differences between right and left femurs for each variable using three imaging modalities (radiography, DXA and computed tomography). These sample size calculations would be useful for investigators in planning their studies based on paired analysis. According to Guller and Oertli (2005), considerations of sample size computation have gained increasing importance in the medical literature, where insufficient sample sizes limit the quality of inferences drawn from research studies due to low power. To this end, the specific aims of this study were to (a) define the intra-subject variation in structural, biomechanical, geometric, and densitometric for a group of femurs from otherwise healthy adult males (mostly Caucasian), (b) determine the relative magnitude of variation in bilateral asymmetry vs. accuracy and precision of imaging modality, and (c) provide sample size requirements for planning future research studies.

2. Materials and methods

Twenty matched pairs of fresh-frozen adult cadaveric femurs were retrieved for osteoarticular allograft implantation (New England Organ Bank, Boston, MA, USA). The specimens were screened for fracture, tumors, and congenital abnormalities, and were rejected for implantation due to bacterial or viral contamination. Of the 20 femur pairs, 19 were from male donors and 1 from a female donor, of which 18 were Caucasians and 2 were African Americans. Mean age of donors was 43.1 ± 12.5 years (range 18–60), height was 176 ± 8 cm (range 157–188), and body mass was 92 ± 28 kg (52–136). The femurs were wrapped in physiologic saline soaked gauze and stored in airtight plastic bags at -20°C .

2.1. Radiological assessment

Orthogonal radiography, DXA, and quantitative computed tomography (QCT) studies were completed for all femoral pairs. The imaging sequence protocol consisted of submerging the femurs in a 0.9% saline bath in acrylic fluid tight chambers constructed to minimize biohazard exposure, with a lucite box cover to simulate overlying soft-tissues for the DXA sequence (Chinander et al., 1999). Plain radiographs were taken in the anteroposterior (AP) and medial-lateral (LAT) projections from the mid-diaphysis to superior femoral head (Fig. 1a) with 83.6 ± 1.98 kVp, 0.66 ± 0.09 mA s, 1.12 ± 0.12 mag, and 114 cm film-focal distance settings (Optimus; Philips Medical Systems, Eindhoven, The Netherlands). A geometric phantom made of aluminum was used to scale the data from the plain radiographs. DXA images were collected in the AP projection from the mid-diaphysis to the superior femoral head (Fig. 1b) using single beam hip mode, 15.25×10.78 cm, 0.1 mm spacing, 0.09 mm point with repeat registration settings (Hologic QDR 2000+, Waltham, MA, USA). BMD (g cm^{-2}) and BMC (g) were calculated for the entire ROI, femoral neck (FN), Ward's triangle (WT), trochanteric, and intertrochanteric (IT) regions.

In order to mimic the *in vivo* orientation of the femurs for plain radiography and DXA imaging, the posterior aspects of the condyles were aligned on the surface of the table and then rotated 15° in anterior rotation. This angle was measured with a compass to the line of the center of the femoral head.

QCT imaging was performed using a high-speed helical CT scanner with 3 mm thick slices spaced 3 mm apart, oriented perpendicular to the diaphyseal axis with 0.5 mm pixel resolution, standard reconstruction, and a bone algorithm window (GE Highlight Advantage™, Wakesha, WI, USA). Six solid hydroxyapatite (HA) phantoms of known densities (0.003, 0.078, 0.178, 0.538, 1.048, 1.597 g cm^{-3}) were placed in the same image field to convert Hounsfield units to equivalent units of calcium hydroxyapatite bone mineral density. Four of the QCT studies were repeated with a sodium phosphate phantom and cross-calibrated to the calcium hydroxyapatite phantom.

The QCT data sets were bilaterally aligned in the chambers and confirmed symmetric through computer image registration of landmarks using advanced volume visualization tools (AVS 5.0, Advanced Visualizations Systems Inc., Waltham, MA, USA). Radio-opaque catheter beads were attached to nine anatomical landmarks, which were then matched by eye, volume visualization, and concurrent two-dimensional slicing through the image stack with the right femur mirrored and superimposed onto the left. These landmarks included the following:

1. Superior aspect of femoral head.
2. Anterior aspect of mid-facet of head (foveal notch).
3. Anterior point of mid-femoral head (from AP view).
4. Femoral axis line mid-diaphysis.
5. Femoral axis line mid-diaphysis.
6. Femoral axis line mid-diaphysis.
7. Most posterior point of the medial condyle.
8. Most posterior point of the lateral condyle.
9. Most superior point of the intercondylar fossa.

2.2. Anthropometric measurements

Five true anatomic anthropometric dimensions were measured with digital calipers to determine femur size including neck length and width, intertrochanteric length, mid-diaphyseal outer diameter (MDOD), and femoral length (piriformis fossa to trochlear groove) (Fig. 1c). Three of the five anthropometric proportions were measured with digital calipers on geometric phantom calibrated plain films, with the addition of the mid-diaphyseal inner diameter (MDID) and femoral head diameter. Regrettably, the entire length of the femur could not be imaged due to a film size constraint (Fig. 2).

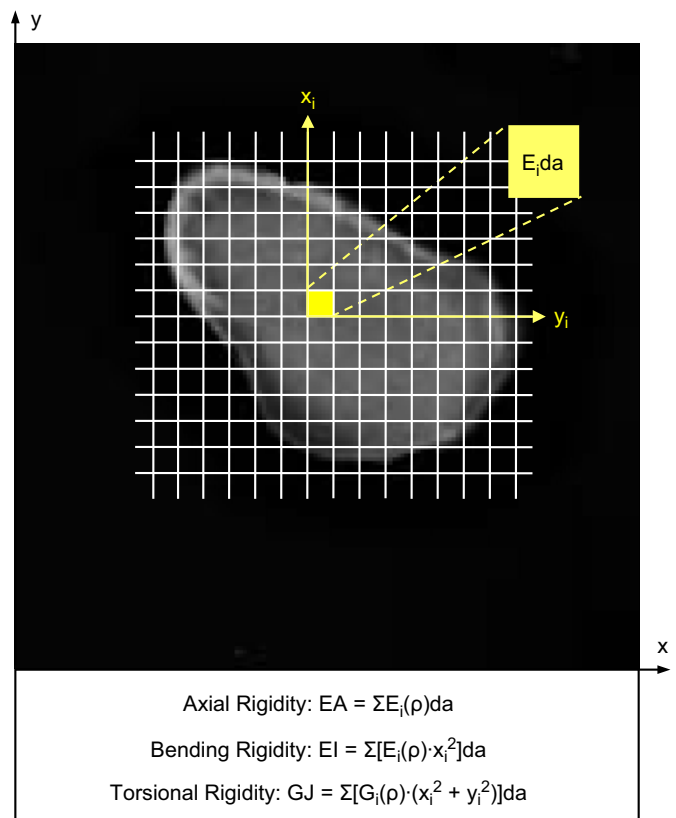


Fig. 2. A schematic demonstration of the QCT-based assessment of structural properties.

Table 1
Physical, DXA based densitometric (BMD), and rigidity (axial and bending) measures of the samples used in this study.

		Variable	<i>L</i> (Mean ± SD)	<i>R</i> (Mean ± SD)	<i>R–L</i> Diff (Mean ± SD)	%DA (%)	<i>T</i> -Test <i>P</i> value	<i>R–L</i> Diff 95% CI ^a
Physical measurements	Anatomic (mm)	Femoral length	422 ± 21	419 ± 21	−3 ± 10	0.0	0.15	(−1.9, 7.8)
		Mid-diaphysis OD	30 ± 3	29 ± 3	−1 ± 2	0.0	0.29	(0.0, 2.0)
		Neck length	25 ± 3	26 ± 4	1 ± 4	0.0	0.55	(−3.0, 1.0)
		Neck width	27 ± 3	27 ± 3	0 ± 3	0.0	0.79	(−1.4, 1.4)
		Interrochanter length	79 ± 5	78 ± 6	−1 ± 4	0.0	0.06	(−1.0, 3.0)
	Radiologic (mm)	Mid-diaphysis OD	29 ± 3	29 ± 3	0 ± 2	0.0	0.74	(−1.0, 1.0)
		Mid-diaphysis ID	12 ± 2	13 ± 4	1 ± 3	0.0	0.64	(−2.4, 0.4)
		Neck length	26 ± 4	25 ± 4	−1 ± 4	0.0	0.23	(−0.9, 2.9)
		Intertrochanter length	78 ± 6	79 ± 5	1 ± 3	0.0	0.34	(−2.4, 0.4)
		Head diameter	46 ± 4	46 ± 4	0 ± 2	0.0	0.85	(−1.0, 1.0)
DXA based bone mineral density [g cm ^{−2}]	Neck	0.84 ± 0.14	0.84 ± 0.13	0.00 ± 0.05	0.0	0.92	(−0.02, 0.02)	
	Trochanteric region	0.78 ± 0.13	0.77 ± 0.11	−0.01 ± 0.04	0.0	0.61	(0.0, 0.03)	
	Intertrochanteric region	1.16 ± 0.17	1.15 ± 0.17	−0.01 ± 0.05	0.0	0.34	(−0.01, 0.03)	
	Total	1.01 ± 0.15	1.00 ± 0.14	−0.01 ± 0.04	0.0	0.4	(−0.01, 0.03)	
	Subcapital	688 ± 187	658 ± 207	−30 ± 120	0.0	0.30	(−28.0, 88.0)	
Axial rigidity [N]	Base of neck	1054 ± 385	990 ± 365	−64 ± 162	0.0	0.11	(−14.0, 142.0)	
	Intertrochanter	2324 ± 765	2261 ± 774	−63 ± 240	0.0	0.28	(−53.0, 179.0)	
	Subtrochanter	4691 ± 1001	4533 ± 1038	−158 ± 450	0.0	0.16	(−59.0, 375.0)	
	Mid-diaphysis	6545 ± 993	6392 ± 1029	−153 ± 333	0.0	0.08	(−7.4, 313.4)	
	Subcapital	0.082 ± 0.027	0.077 ± 0.029	−0.004 ± 0.018	0.0	0.31	(0.0, 0.01)	
Bending rigidity [N m ²]	Base of neck	0.129 ± 0.046	0.124 ± 0.046	−0.005 ± 0.022	0.0	0.30	(0.0, 0.02)	
	Intertrochanter	0.177 ± 0.054	0.169 ± 0.050	−0.007 ± 0.022	0.0	0.16	(0.0, 0.02)	
	Subtrochanter	0.347 ± 0.091	0.332 ± 0.087	−0.014 ± 0.039	0.0	0.13	(0.0, 0.03)	
	Mid-diaphysis	0.392 ± 0.095	0.385 ± 0.097	−0.007 ± 0.039	0.0	0.45	(0.0, 0.03)	

OD=outer diameter; ID=inner diameter; CI=confidence interval; %DA=percent difference for asymmetry.

^a Confidence intervals were calculated using the *t* distribution for defining the normal range of bilateral asymmetry, where 95% CI=mean difference ± $t_{0.025,(n-1)} \times \text{SD}/\sqrt{n}$ (Montgomery, 2001).For physical measurements: $n=20$, $t_{0.025,(n-1)}=2.093$ for DXA based BMC: $n=19$, $t_{0.025,(n-1)}=2.101$ for axial and bending rigidities: $n=18$, $t_{0.025,(n-1)}=2.110$.

2.3. Assessment of QCT-based structural properties

This process has been detailed elsewhere. Please refer to Appendix A for full description of the processes implemented for this portion of the study (Whealan et al., 2000; Hong et al., 2004).

2.4. Statistical analysis

Power analysis indicated that a minimum of 20 patients would provide 80% statistical power ($\alpha=0.05$, $\beta=0.20$) to detect a mean difference of 1% between left and right femurs based on paired analysis assuming a standard deviation of 1.5% (standardized effect size=0.67) (version 7.0, nQuery Advisor, Statistical Solutions, Saugus, MA) (Hulley et al., 2001). All physical, densitometric, and rigidity measurements were assessed for normality using the Kolmogorov–Smirnov goodness-of-fit and no significance departures were identified for any variable (Riffenburgh, 2006). Therefore, bilateral asymmetry was evaluated by paired *T*-tests (parametric approach since assumptions of normality were supported), and the *T*-distribution was used to determine the 95% confidence intervals (CI), which defined the normal ranges for each variable (Montgomery, 2001). Results of the *T*-testing provide information as to whether the left–right difference is significantly different from 0 in the population. Sample size requirements based on detecting left–right differences of 5% and 10% and the corresponding effect sizes for planning future studies using paired samples (Pearson and Hartley, 1976; Montgomery, 2001). In addition, we calculated the relative percent differences for asymmetry (%DA), which facilitate comparisons to other published data. A two-tailed value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

A subset of 5 specimens, selected at random, was subjected to a reproducibility study, where anthropometric measurements were repeated 3 times. DXA and QCT images were obtained three times, by replacing and reimaging the specimen in the imaging surface/gantry each time (all performed by the same operator) and recalculating densitometric and structural properties.

3. Results

Normative structural rigidity and the bilateral variation of the five anatomic sites (subcapital, base of neck, intertrochanter, subtrochanter and mid-diaphysis) determined by QCT measurements are presented in Table 1 and Figs. 5 and 6. Previous authors have reported similar structural measurements (Lotz et al., 1991; Griffin et al., 1993). We found no significant differences in axial or bending rigidity between left and right femurs ($p > 0.10$ for all cases). For example, the left–right difference in axial rigidity for the subcapital region was 30 ± 120 N. In addition, in planning a study a total of 28 femur pairs would provide 80% power to detect a 10% *L–R* difference in the subcapital region. The effect size for this calculation is based on 10% of the average axial rigidity of both left and right femurs $(688+658)/2=673$ divided by the SD of the left–right difference $(67/120=0.56)$. Similarly, for bending rigidity the left–right difference averaged 0.004 ± 0.018 N m² for the subcapital region. To achieve 80% power for an investigation, a sample size of 43 femur pairs would be required to detect 10% bilateral asymmetry, where the effect size is calculated as 10% of the average bending rigidity divided by the SD of the left–right difference (i.e., $0.082+0.077)/2=0.079/0.018$ or 0.44).

Normative dimensions and bilateral variation of the true anatomic anthropometric dimensions determined by caliper measurements, both directly on the specimens and on the corresponding orthogonal radiographs, are presented in Table 1 and Fig. 3. Anthropometric measurements for this sample were in accordance with reported measures as noted in the table; thus,

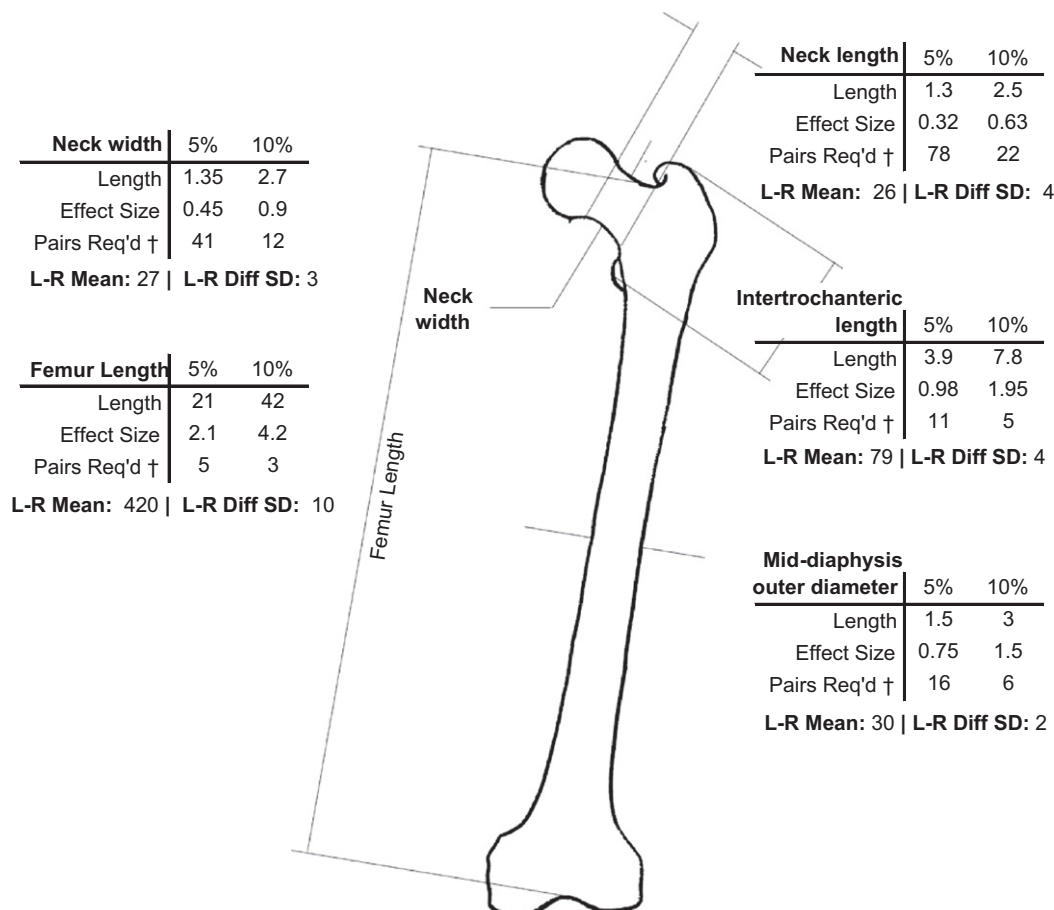


Fig. 3. This figure presents the number of specimens needed to detect differences of 5% and 10% in bilateral symmetry of anthropomorphic measures between left and right femurs. The number of femur pairs required are calculated based on 80% power using a two-tailed paired *T*-test[†] (*L–R* mean=mean value of left and right femur, *L–R* diff SD=standard deviation of the difference between left and right femurs).

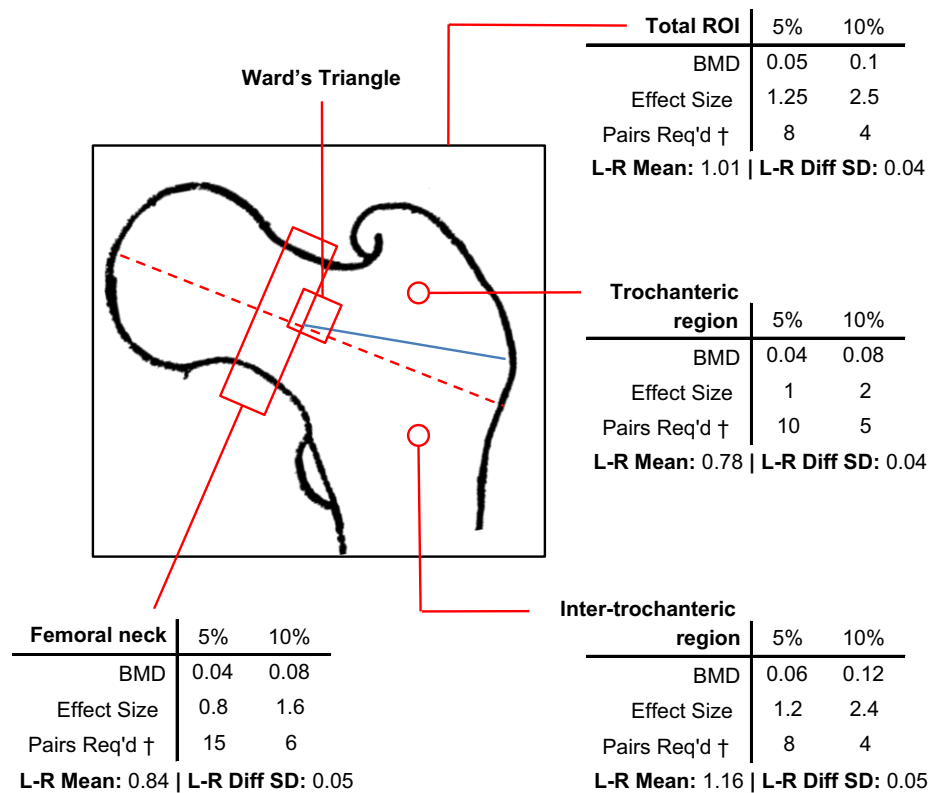


Fig. 4. This figure presents the number of specimens needed to detect differences of 5% and 10% in bilateral symmetry of DXA-based densitometric measures between left and right femurs. The number of femur pairs required are calculated based on 80% power using a two-tailed paired *T*-test† (*L-R* mean=mean value of left and right femur, *L-R* diff SD=standard deviation of the difference between left and right femurs).

supporting that our sample pool adequately represented a normal population. No significant differences were observed between left and right femurs ($p > 0.05$ for all cases) with respect to anthropometric and radiological variables. Others have reported similar values (Noble et al., 1988).

Normative DXA generated BMD and bilateral variation of the femoral neck, trochanteric region, intertrochanteric region, and total ROI measurements are presented in Table 1 and Fig. 4. Similar values have been reported by other researchers (Cheng et al., 1998; Mazess and Barden, 1999). In planning a research study, investigators aiming to detect a 10% difference in density based on DXA for the neck region between left and right femurs would need to evaluate a minimum of 6 femur pairs to be able to detect this magnitude of a difference (effect size $0.08/0.05 \text{ g cm}^{-2} = 1.6$) with 80% power (Figs. 5 and 6).

Reproducibility studies on a subset of specimens indicated that intra-operator variability was less than half of the reported bilateral variabilities (anthropometric, structural, and densitometric) suggesting that the overall consistency of the measurements demonstrated reasonable reproducibility.

4. Discussion

Our results suggest that the overall right and left femur geometric, densitometric, and structural properties are not significantly different from one another. However, absolute left-right differences for individual patients can be significant, especially in the case of structural rigidity properties, and should be considered in clinical and research studies. Individual bilateral variation can affect studies relying on the contralateral femur as an intra-subject control (Noble et al., 1988; Rice et al., 1988; Lotz

et al., 1990; Snyder and Schneider, 1991a,b; Cheal et al., 1993; Griffin et al., 1993; Bryan et al., 1996; Cheng et al., 1998; Chinander et al., 1999; Mazess and Barden, 1999; Iida et al., 2000; Whealan et al., 2000; Keyak et al., 2001; Guller and Oertli, 2005).

The true anatomical anthropometric measurements of the left femur were less than 10% different from the right femur for the majority of the cases. The few cases that demonstrated bilateral asymmetry were in regions where measurement values were dependent upon precise registration of functional landmarks (i.e., the femoral neck). The geometric size measurements were within approximately 1 mm of the plain radiograph film measurements, supporting that each was acceptable for the determination of basic femoral dimensions. The variation in the bilateral dimensions falls within the tolerance of the accuracy and precision of plain film readings estimated to be approximately 2.9% (Kouloulas et al., 2004).

DXA analysis provided sample means in excellent agreement with those published for similar cohorts (Cheng et al., 1998; Mazess and Barden, 1999). The majority of the cases were bilaterally symmetric for the regions. However, approximately 25% of the cases were asymmetric in one or more regions. These asymmetric values were comparable to differences reported by Mazess et al. (2000), with a similar cohort of normal adults. It is noteworthy that the large variation in Ward's triangle BMD was primarily due to inability to measure the same region of interest in a repeatable fashion and therefore was not reported. The observed deviation from bilateral symmetry for the variables measured in this study exceed reported (Griffin et al., 1993; Sievanen et al., 1993) densitometric measurement precision for DXA (1–3%, 1.3% at the femoral neck (Sievanen et al., 1992). Routinely, only one limb is scanned using DXA. In patient cases where geometric and densitometric bilateral variation is large, single hip DXA scanning may over- or under-estimate BMD, BMC,

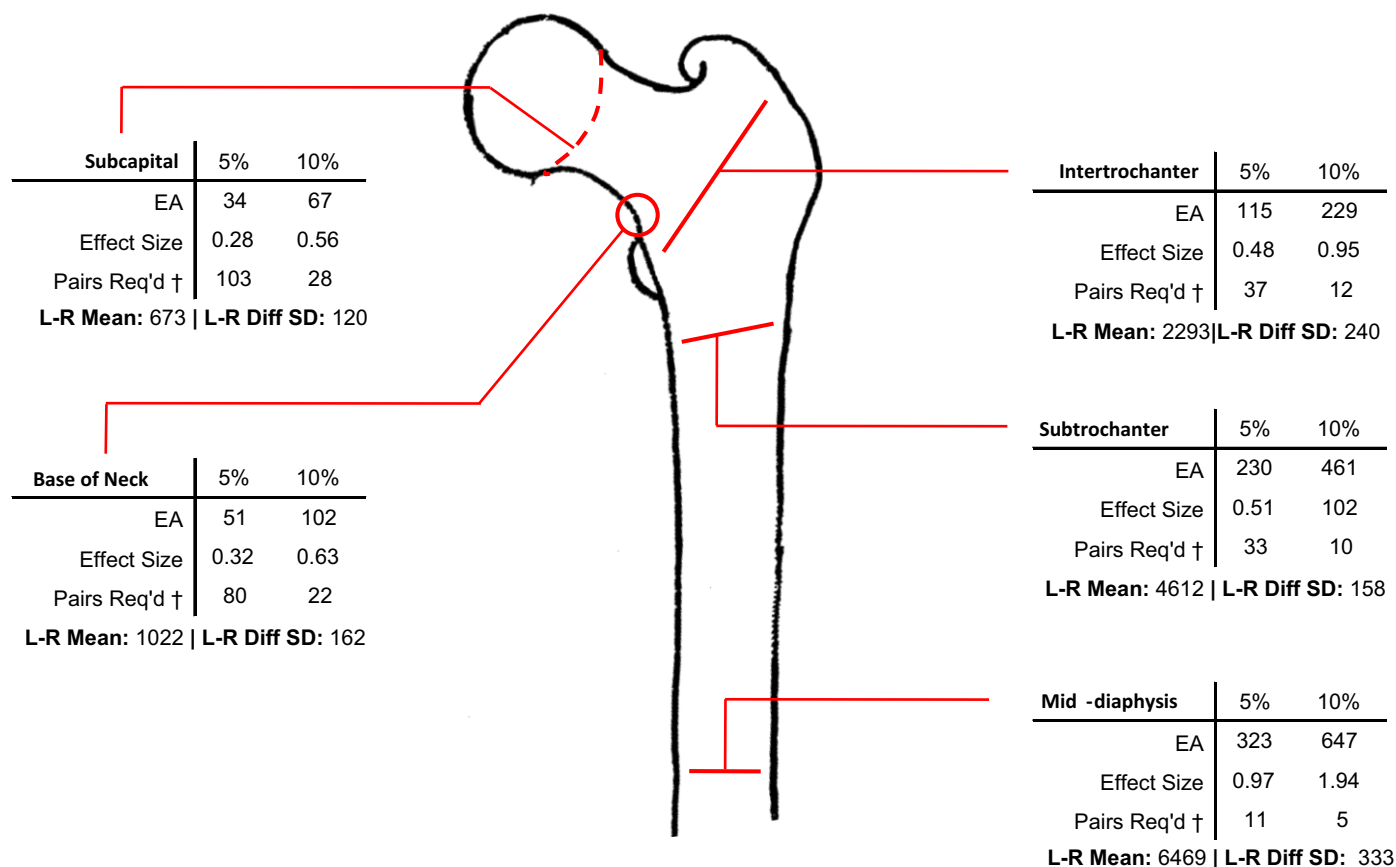


Fig. 5. The figure presents the number of specimens needed to detect differences of 5% and 10% in bilateral symmetry of QCT-based structural axial rigidity measures between left and right femurs. The number of femur pairs required are calculated based on 80% power using a two-tailed paired *T*-test[†] (L-R mean=mean value of left and right femur, L-R diff SD=standard deviation of the difference between left and right femurs).

and fracture risk. These variations support the importance of bilateral scanning with matched registration. Recent investigations into the use of a lower limb positioner for DXA imaging of both femurs have started to emerge.

The cross-sectional structural properties in our study were in good agreement with Ruff and Hayes (1984). Studies of structural property differences as a function of age and sex-related changes primarily focus on inertia and cross-sectional area (Martin and Atkinson, 1977; Ruff and Hayes, 1988; Stein et al., 1998). It should be noted that density reflects material composition but fails to take into account how the material is distributed in space. The geometric properties are very important, and together, the material properties (represented by density) and geometric properties (represented by area and moment of inertia) determine the structural properties of the femur, which in turn govern the load capacity of the femur. The 10–15% differences in structural properties are relatively large. To understand one way to interpret the significance of the magnitude of the differences between left and right femurs, we can review the findings of Oden et al. (1999) who demonstrated that a 5% increase in density of the femur could result in a 5% increase in failure load. Therefore, the extent of asymmetry measured in these specimens would significantly affect the stress and strain distributions. Based upon asymmetry of structural properties, approximately 40% of the specimens could have greater than 5% difference in failure load. In clinical follow-up of pediatric benign tumors of the femur, we found that a difference greater than 35% in structural rigidities was necessary to discriminate fracture risk in children with benign bone tumors (Snyder et al., 2006). Fracture predictions based upon structural analysis of DXA or QCT data must exceed naturally occurring

differences in bilateral symmetry to be considered significant (Mourtada et al., 1996; Lochmuller et al., 2000). The observed variation from bilateral symmetry for the rigidities measured in this study exceeded reported average measurement accuracy for QCT (7%) (Rubin et al., 1992).

Non-invasive image guided techniques for reconstruction of the hip (Bargar et al., 1998; DiGioia et al., 1998) should assess the bilateral variation of the femur before numerical milling, or cutting of the bone with computer driven programs utilizing contralateral, or normative data for the femur. The use of the contralateral femur for a normal map to prepare or assess the affected femur will work for some but not all cases. This element must be factored in when the contralateral femur is used to evaluate fracture risk, disease progression, or treatment efficacy in the clinical or laboratory setting.

The main limitation of our study was our small sample size. Only 20 pairs of matched femurs were evaluated. In addition, only bilateral variation of the femur was evaluated. While several studies have examined bilateral variation at other anatomic sites, a comprehensive evaluation of geometric, densitometric, and structural bilateral variation in all long bones using plain radiography, DXA, and QCT has not been performed. Future studies can evaluate other anatomic sites; however, most research and clinical studies focus on the femur and its impact on fracture risk analysis and femoral component design. Also, our study obtained perfect matched registration of nine anatomic landmarks for all imaging modalities. Such a precise registration scheme is impossible in the clinical setting. However, improvements in post-image processing, advancements in macro- and microstructure imaging (Rubin et al., 1992), and novel and comprehensive DXA ROI's (Takada et al., 1997; Prevrhal et al., 2004)

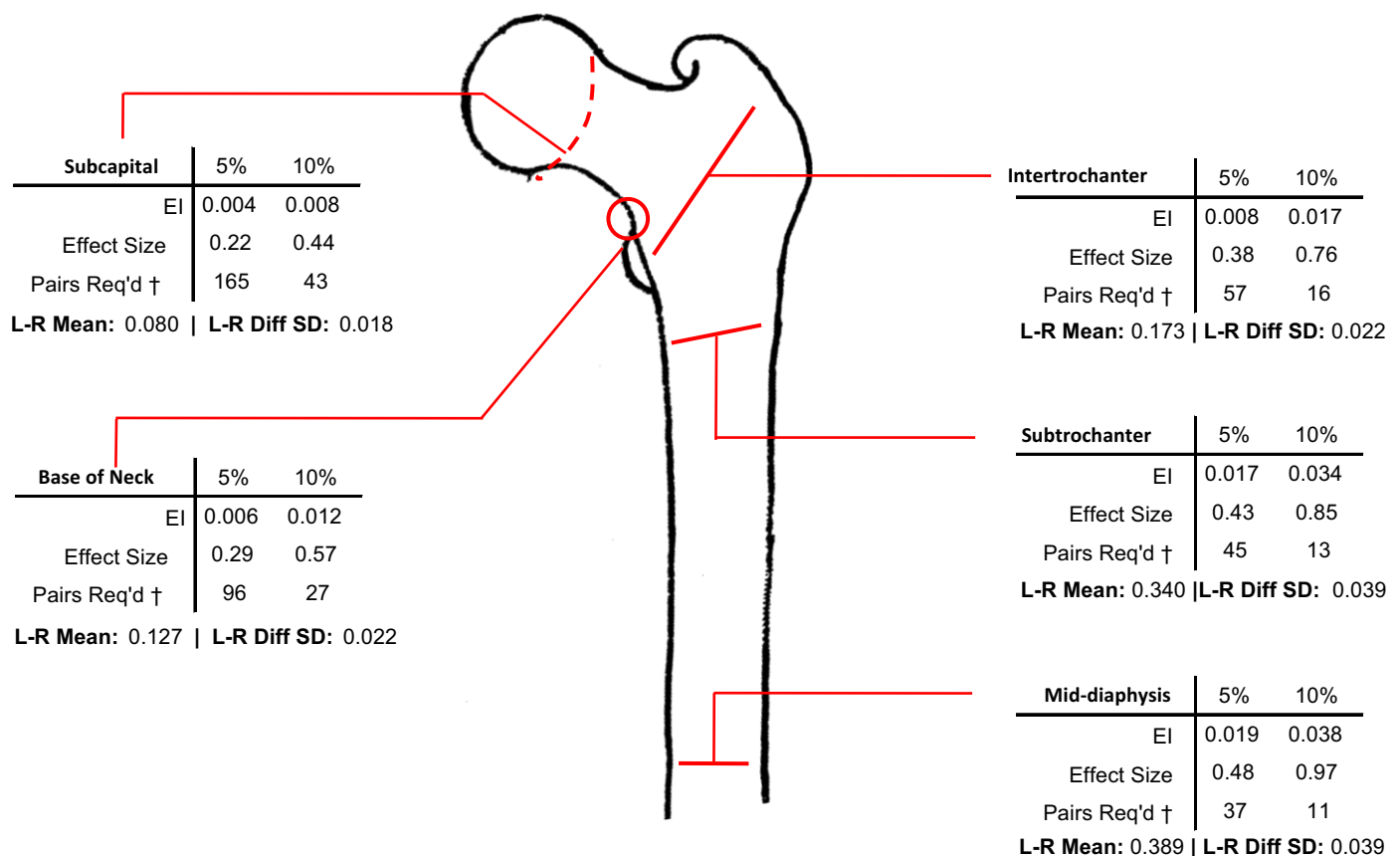


Fig. 6. This figure presents the number of specimens needed to detect differences of 5% and 10% in bilateral symmetry of QCT-based structural bending rigidity measures between left and right femurs. The number of femur pairs required are calculated based on 80% power using a two-tailed paired *T*-test[†] (*L-R* mean = mean value of left and right femur, *L-R* diff SD = standard deviation of the difference between left and right femurs).

will aid in registration and analysis. While data on limb dominance, recent and accumulated activity level prior to death, and past medical history may have affected the loading pattern of the femur would have been interesting covariates, this data was not available to us.

Despite the study's limitations, it was the first comprehensive evaluation of geometric, densitometric, and structural bilateral variation using multiple imaging modalities. Previous studies have focused primarily on DXA analysis alone. This study provides both researchers and clinicians with sample size requirements in designing future studies for assessing biomechanical properties of paired femurs. To detect a difference of 5% or 10% between femoral pairs researchers are provided with sample sizes for attaining 80% power.

In conclusion, there are no significant differences between the left and right proximal femurs based on geometric, densitometric, and structural measurements. However, large asymmetries were found for individual pairs. Our data provides further support for the use of contralateral femurs as appropriate controls for each other. However, when using the contralateral femur as an intra-subject control, the number of femur pairs required to assess significant changes in anatomic dimensions and structural properties induced by a tumor, infection, fracture, or implanted device can range from 3 to 165 pairs depending on the desired effect size or sensitivity (5% or 10% difference).

Conflict of interest

None to report.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jbiomech.2010.02.032.

References

- Adachi, J.D., 1996. The correlation of bone mineral density and biochemical markers to fracture risk. *Calcif. Tissue Int.* 59, 16–19.
- Alfredson, H., Nordstrom, P., Lorentzon, R., 1996. Total and regional bone mass in female soccer players. *Calcif. Tissue Int.* 59, 438–442.
- Bainbridge, K.E., Sowers, M., Lin, X., Harlow, S.D., 2004. Risk factors for low bone mineral density and the 6-year rate of bone loss among premenopausal and perimenopausal women. *Osteoporos. Int.* 15, 439–446.
- Bargar, W.L., Bauer, A., Borner, M., 1998. Primary and revision total hip replacement using the robodoc system. *Clin. Orthop. Relat. Res.*, 82–91.
- Bryan, J.M., Sumner, D.R., Hurwitz, D.E., Tompkins, G.S., Andriacchi, T.P., Galante, J.O., 1996. Altered load history affects periprosthetic bone loss following cementless total hip arthroplasty. *J. Orthop. Res.* 14, 762–768.
- Cheal, E.J., Hipp, J.A., Hayes, W.C., 1993. Evaluation of finite element analysis for prediction of the strength reduction due to metastatic lesions in the femoral neck. *J. Biomech.* 26, 251–264.
- Cheng, X.G., Lowet, G., Boonen, S., Nicholson, P.H., Van der Perre, G., Dequeker, J., 1998. Prediction of vertebral and femoral strength in vitro by bone mineral density measured at different skeletal sites. *J. Bone Miner. Res.* 13, 1439–1443.
- Chinander, M.R., Giger, M.L., Martell, J.M., Jiang, C., Favus, M.J., 1999. Computerized radiographic texture measures for characterizing bone strength: a simulated clinical setup using femoral neck specimens. *Med. Phys.* 26, 2295–2300.
- Cody, D.D., McCubbrey, D.A., Divine, G.W., Gross, G.J., Goldstein, S.A., 1996. Predictive value of proximal femoral bone densitometry in determining local orthogonal material properties. *J. Biomech.* 29, 753–761.
- DiGioia, A.M., Jaramaz, B., Blackwell, M., Simon, D.A., Morgan, F., Moody, J.E., Nikou, C., Colgan, B.D., Aston, C.A., Labarca, R.S., Kischell, E., Kanade, T., 1998. The Otto Aufranc Award. Image guided navigation system to measure intraoperatively acetabular implant alignment. *Clin. Orthop. Relat. Res.*, 8–22.

- Freedman, D.M., Edwards Jr., G.S., Willems, M.J., Meals, R.A., 1998. Right versus left symmetry of ulnar variance. A radiographic assessment. *Clin. Orthop. Relat. Res.*, 153–158.
- Gonzalez Della Valle, A., Slullitel, G., Piccaluga, F., Salvati, E.A., 2005. The precision and usefulness of preoperative planning for cemented and hybrid primary total hip arthroplasty. *J. Arthroplasty* 20, 51–58.
- Griffin, M.G., Kimble, R., Hopfer, W., Pacifici, R., 1993. Dual-energy X-ray absorptiometry of the rat: accuracy, precision, and measurement of bone loss. *J. Bone Miner. Res.* 8, 795–800.
- Gualdi-Russo, E., 1998. Study on long bones: variation in angular traits with sex, age, and laterality. *Anthropol. Anz.* 56, 289–299.
- Culler, U., Oertli, D., 2005. Sample size matters: a guide for surgeons. *World J. Surg.* 29, 601–605.
- Gumustekin, K., Akar, S., Dane, S., Yildirim, M., Seven, B., Varoglu, E., 2004. Handedness and bilateral femoral bone densities in men and women. *Int. J. Neurosci.* 114, 1533–1547.
- Haapasalo, H., Kannus, P., Sievanen, H., Pasanen, M., Uusi-Rasi, K., Heinonen, A., Oja, P., Vuori, I., 1998. Effect of long-term unilateral activity on bone mineral density of female junior tennis players. *J. Bone Miner. Res.* 13, 310–319.
- Hiramoto, Y., 1993. Right–left differences in the lengths of human arm and leg bones. *Kaibogaku Zasshi* 68, 536–543.
- Hong, J., Cabe, G.D., Tedrow, J.R., Hipp, J.A., Snyder, B.D., 2004. Failure of trabecular bone with simulated lytic defects can be predicted non-invasively by structural analysis. *J. Orthop. Res.* 22, 479–486.
- Hulley, S.B., Cummings, S.R., Browner, W.S., Grady, W., Hearst, N., Newman, T.B., 2001. *Designing Clinical Research: An Epidemiologic Approach*. Lippincott and Williams, Philadelphia.
- Iida, Y., Kuroda, T., Kitano, T., Mizuno, K., 2000. DEXA-measured bone density changes over time after intertrochanteric hip fractures. *Kobe J. Med. Sci.* 46, 1–12.
- Kannus, P., Haapasalo, H., Sievanen, H., Oja, P., Vuori, I., 1994. The site-specific effects of long-term unilateral activity on bone mineral density and content. *Bone* 15, 279–284.
- Keyak, J.H., Rossi, S.A., Jones, K.A., Les, C.M., Skinner, H.B., 2001. Prediction of fracture location in the proximal femur using finite element models. *Med. Eng. Phys.* 23, 657–664.
- Khunkitti, N., Aswaboonyalert, N., Songpatanasilp, T., Pipithkul, S., 2000. Fracture threshold in the Thai elderly and bone mineral density evaluation. *J. Bone Miner. Metab.* 18, 96–100.
- Kouloulis, V.E., Matsopoulos, G., Kouvaris, J.R., Antypas, C., Uzunoglu, N.C., Varela, M.N., Metafa, A., Sandilos, P., Vlahos, L.J., 2004. Limitations of quantitative bone-mass measurements using assessments of first-order statistics of grey-level histograms in plain radiographs. *Acta Radiol.* 45, 197–203.
- Livshits, G., Yakovenko, K., Kletselman, L., Karasik, D., Kobylansky, E., 1998. Fluctuating asymmetry and morphometric variation of hand bones. *Am. J. Phys. Anthropol.* 107, 125–136.
- Lochmuller, E.M., Miller, P., Burklein, D., Wehr, U., Rambeck, W., Eckstein, F., 2000. In situ femoral dual-energy X-ray absorptiometry related to ash weight, bone size and density, and its relationship with mechanical failure loads of the proximal femur [In Process Citation]. *Osteoporos. Int.* 11, 361–367.
- Lotz, J., Gerhart, T., Hayes, W., 1990. Mechanical properties of trabecular bone from the proximal femur: a quantitative CT study. *J. Comp. Assist. Tomogr.* 14, 107–113.
- Lotz, J., Gerhart, T., Hayes, W., 1991. Mechanical properties of metaphyseal bone in the proximal femur. *J. Biomech.* 24, 317–329.
- Martin, R., Atkinson, P., 1977. Age and sex-related changes in the structure and strength of the human femoral shaft. *J. Biomech.* 10, 223–231.
- Mazess, R.B., Barden, H., 1999. Bone density of the spine and femur in adult white females. *Calcif. Tissue Int.* 65, 91–99.
- Mazess, R.B., Nord, R., Hanson, J.A., Barden, H.S., 2000. Bilateral measurement of femoral bone mineral density. *J. Clin. Densitom.* 3, 133–140.
- Montgomery, D.C., 2001. *Design and Analysis of Experiments*. John Wiley New York.
- Mourtada, F.A., Beck, T.J., Hauser, D.L., Ruff, C.B., Bao, G., 1996. Curved beam model of the proximal femur for estimating stress using dual-energy X-ray absorptiometry derived structural geometry. *J. Orthop. Res.* 14, 483–492.
- Noble, P.C., Alexander, J.W., Lindahl, L.J., Yew, D.T., Granberry, W.M., Tullios, H.S., 1988. The anatomic basis of femoral component design. *Clin. Orthop. Relat. Res.*, 148–165.
- Noble, P.C., Sugano, N., Johnston, J.D., Thompson, M.T., Conditt, M.A., Engh Sr., C.A., Mathis, K.B., 2003. Computer simulation: how can it help the surgeon optimize implant position? *Clin. Orthop. Relat. Res.* 242–252.
- Oden, Z.M., Selvitelli, D.M., Bouxsein, M.L., 1999. Effect of local density changes on the failure load of the proximal femur. *J. Orthop. Res.* 17, 661–667.
- Pearson, E.S., Hartley, H.O., 1976. *Biometrika Tables for Statisticians*. Cambridge Univ Pr (Sd).
- Plochocki, J.H., 2004. Bilateral variation in limb articular surface dimensions. *Am. J. Hum. Biol.* 16, 328–333.
- Prevhal, S., Meta, M., Genant, H.K., 2004. Two new regions of interest to evaluate separately cortical and trabecular BMD in the proximal femur using DXA. *Osteoporos. Int.* 15, 12–19.
- Rice, J.C., Cowin, S.C., Bowman, J.A., 1988. On the dependence of the elasticity and strength of cancellous bone on apparent density. *J. Biomech.* 21, 155–168.
- Riffenburgh, R.H., 2006. *Statistics in Medicine*. Elsevier, New York.
- Rubin, P.J., Leyvraz, P.F., Aubaniac, J.M., Argenson, J.N., Esteve, P., de Roguin, B., 1992. The morphology of the proximal femur. A three-dimensional radiographic analysis. *J. Bone Jt. Surg. Br.* 74, 28–32.
- Ruff, C., Hayes, W., 1988. Sex differences in age-related remodeling of the femur and tibia. *J. Orthop. Res.* 6, 886–896.
- Ruff, C.B., Hayes, W.C., 1984. Age changes in geometry and mineral content of the lower limb bones. *Ann. Biomed. Eng.* 12, 573–584.
- Sievanen, H., Kannus, P., Oja, P., Vuori, I., 1993. Precision of dual energy X-ray absorptiometry in the upper extremities. *Bone Miner.* 20, 235–243.
- Sievanen, H., Oja, P., Vuori, I., 1992. Precision of dual-energy X-ray absorptiometry in determining bone mineral density and content of various skeletal sites. *J. Nucl. Med.* 33, 1137–1142.
- Snyder, B.D., Hauser-Kara, D.A., Hipp, J.A., Zurakowski, D., Hecht, A.C., Gebhardt, M.C., 2006. Predicting fracture through benign skeletal lesions with quantitative computed tomography. *J. Bone Jt. Surg. Am.* 88, 55–70.
- Snyder, S., Schneider, E., 1991a. Estimation of mechanical properties of cortical bone by computed tomography. *J. Orthop. Res.* 9, 422–431.
- Snyder, S.M., Schneider, E., 1991b. Estimation of mechanical properties of cortical bone by computed tomography. *J. Orthop. Res.* 9, 422–431.
- Stein, M.S., Thomas, C.D., Feik, S.A., Wark, J.D., Clement, J.G., 1998. Bone size and mechanics at the femoral diaphysis across age and sex. *J. Biomech.* 31, 1101–1110.
- Strecker, W., Keppler, P., Gebhard, F., Kinzl, L., 1997. Length and torsion of the lower limb. *J. Bone Jt. Surg. Br.* 79, 1019–1023.
- Takada, M., Grampp, S., Ouyang, X., Engelke, K., Genant, H.K., 1997. A new trabecular region of interest for femoral dual X-ray absorptiometry: short-term precision, age-related bone loss, and fracture discrimination compared with current femoral regions of interest. *J. Bone Miner. Res.* 12, 832–838.
- Vrahoriti, H., Damlakis, J., Papadokostakis, G., Hadjipavlou, A., Gourtsoyannis, N., 2004. Bilateral variation in radial bone speed of sound. *Eur. Radiol.* 14, 953–958.
- Whealan, K.M., Kwak, S.D., Tedrow, J.R., Inoue, K., Snyder, B.D., 2000. Noninvasive imaging predicts failure load of the spine with simulated osteolytic defects. *J. Bone Jt. Surg. Am.* 82, 1240–1251.
- Yang, R., Tsai, K., Chieng, P., Liu, T., 1997. Symmetry of bone mineral density at the proximal femur with emphasis on the effect of side dominance. *Calcif. Tissue Int.* 61, 189–191.