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VALIDATING THE USE OF PERIPHERAL BONE SITES TO PREDICT THE RISK OF FEMORAL NECK FRACTURE

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ABSTRACT

As the population of older adults increases, osteoporosis and osteoporotic fractures become more and more of a concern for our health care system. Osteoporosis is characterized by a lower bone mineral density (BMD), which typically occurs during the aging process. BMD is typically measured using dual x-ray absorptiometry (DXA), which is subject to error based on bone size due to its two-dimensional nature. A solution to this problem is peripheral quantitative computed tomography (pQCT), which is a three-dimensional imaging method that exposes the patient to minimal peripheral radiation, while increasing the accuracy of the measurement and diagnosis. The purpose of this study was to determine which parameters at the distal radius and distal tibia would best predict femoral neck parameters. pQCT was used to measure parameters at the distal tibia, distal radius, and femoral neck. Parameters at the distal tibia and distal radius were correlated to find the best model to predict femoral neck fractures. The parameters that significantly correlated to trochanteric BMD were tibial polar stress-strain index (R = 0.770), tibial orthogonal sectional stress-strain indices (R = 0.803 and R = 0.772 for x-coordinate and y-coordinate, respectively), tibial total BMD (R = 0.824), radial total bone mineral content (R = 0.732), and radial BMD (R = 0.758). The parameter that significantly correlated to trochanteric trabecular BMD was radial total BMD (0.746). The best prediction of femoral trochanter BMD was given by the tibial x-coordinate sectional stress-strain index alone (R = 0.803). The best prediction of femoral neck BMD was given by the combination of radial cross-sectional moment of inertia, radial total bone mineral content (BMC), and tibial y-coordinate sectional stress-strain index (R = 0.904). The best prediction of femoral trochanter trabecular BMD was given by the combination of tibial total BMD, tibial x- and y-coordinate sectional stress-strain index, radial total BMD, radial cross-sectional moment of inertia, and radial trabecular BMD (R = 1.000). The best prediction of femoral neck trabecular BMD was given by the combination of tibial total BMD, tibial x-coordinate sectional stress-strain index, and radial cross-sectional moment of inertia, total BMD, and total BMC (R = 0.988). And the best prediction of femoral

head trabecular BMD was given by the combination of radial cross-sectional moment of inertia, radial total BMC, and tibial x-coordinate sectional stress-strain index (R = 0.965). The results suggest that there are multiple models to accurately predict parameters at various fracture-prone sites of the femoral neck. This study demonstrates that pQCT scans at the distal radius or distal tibia, along with traditional DXA scans, would give a more complete prediction of femoral neck fracture risk, which can lead to a more accurate diagnosis of osteoporosis. With hip fractures becoming more and more of a health problem in the older population and with all the complications that follow a hip fracture, using a quick pQCT scan as a tool to help accurately predict osteoporosis-related fracture risk could increase early detection and prevent fractures.

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Chapter 1

Introduction

Measurements of Bone Density to Determine Osteoporosis

With the increased number of older adults in our population, osteoporosis and fractures caused by osteoporosis are of increasing concern for health experts. Osteoporotic fractures are accompanied by enormous health care expenditures, loss of productivity, and premature death (Boehm & Link, 2004). Osteoporosis, as defined by the National Institutes of Health (NIH), is a skeletal disorder characterized by weakened bone strength, which increases the risk of fracture. Bone strength includes both bone density and bone quality. Bone mineral density (BMD) accounts for 60% to 80% of bone strength and bone quality accounts for the remaining 20% to 40% (Boehm & Link, 2004). Bone quality describes a number of contributors to bone strength, including microarchitectural aspects, biological turnover, cell viability, damage accumulation, and matrix composition. However, none of these measures are as easy to obtain as bone density, nor is the direct relationship from these measures to fracture as well defined. BMD is simply the mass of bone mineral present in grams per area or volume and can be determined by well-established diagnostic procedures. BMD is usually used to diagnosis osteoporosis because it is easily accessible, has high precision, and correlates well with bone strength and fracture risk.

Typically, BMD is measured by dual x-ray absorptiometry (DXA) or quantitative computed tomography (QCT) (Boehm & Link, 2004). DXA is noninvasive, quick, relatively low cost, and gives only a low radiation dose, but still has a relatively high precision and accuracy (Formica, Nieves, Cosman, Garret, & Lindsay, 1998). DXA is currently considered the “gold standard” in diagnosing osteoporosis. However, DXA is not as precise as some other imagine methods, including computed tomography (CT) (Boehm & Link, 2004). QCT is a highly focused 3-dimensional (3D) x-ray that can

give a 3D rendering of different bone sites. It typically gives more information than DXA, but about a smaller area. QCT provides geometric and volumetric density information, whereas DXA only provides 2-dimensional information (Sheu et al., 2011). After a person has been shown to have a decreased BMD and been diagnosed with osteoporosis, there are several preventative medications that typically decrease the risk of fracture. These medications include calcium, vitamin D, bisphosphonates, selective estrogen receptor modulators, estrogen, and calcitonin (Boehm & Link, 2004). However, these drugs can be costly and can have negative side effects.

The most common osteoporotic fractures are of the hip, distal radius, and spine. Fractures of the hip are typically the most serious, with a mortality rate around 25% during the year following the fracture (Boehm & Link, 2004). Compared to young and middle-age adults, elderly people are more likely to suffer a hip fracture because of their higher tendency to fall, which results from muscular atrophy and neurological conditions (Guerado et al., 2016). Typically, the older a person is, the greater his or her risk of fracture. With life expectancy increasing all over the world, the number of hip fractures is expected to increase in elderly people (Sheu et al., 2011). Also, women typically have a greater risk of fracture than men because women have a decrease in estrogen levels that occur during menopause, leading to a decrease in BMD. But, interestingly, men who have suffered a hip fracture have a higher mortality rate than women who suffer a hip fracture (Sheu et al., 2011). Once a person has suffered a hip fracture, he or she is two to three times more likely to suffer a later fracture. The increased risk of fracture is thought to be from the further decrease in bone mass of the affected leg, causing side-to-side differences between the legs leading to further instability (Mikkola et al., 2007). Hip fractures in osteoporotic patients usually happen as a result of a small force or moderate trauma on the femur. The trauma could be from falling or simply walking if the BMD is low enough. A fracture can severely decrease the person's mobility and cause him or her to be afraid of moving at all, only diminishing his or her health and bone quality further (Mikkola et al., 2007).

A decrease in BMD is correlated to an increased risk of osteoporotic fractures, so the less dense the bone, the more likely it is to fracture (Guerado et al., 2016). BMD is not the only factor that affects hip strength and fracture risk; strength also depends on 3D shape, the distribution of bone material within the entire structure, the micro-architectural properties of the distributed bone material, loading conditions, and structural geometric parameters, which include hip axis length, femoral neck diameter, cross-sectional moment of inertia, and cortical wall thickness (Le Bras et al., 2006). Measuring these characteristics of bone strength and geometry might even provide a more thorough understanding of bone strength and better fracture prediction beyond BMD alone (Sheu et al., 2011). In addition, the imprecise nature of DXA, compared to other imaging, suggests a more detailed imaging method may provide a better measure of fracture risk, especially in the femur.

Imaging Methods

DXA of the lumbar spine and proximal femur is the best-established technique to measure BMD and diagnose osteoporosis. BMD determined by DXA is a good predictor of fracture risk, and measurements can be performed close to the site of interest, such as the proximal femur. Typically, the most accurate assessment of fracture risk of a certain bone is taken at that bone. For example, the most accurate prediction of hip fracture is a scan of the proximal femur. However, there is an overlap in the BMD results between individuals who have not experienced fractures and those who have, creating controversy on how accurate this method is (Boehm & Link, 2004). The 2 dimensional (2D) scans taken by DXA can be used to estimate skeletal structural 3D parameters, which may help better assess fracture risk along with BMD (Melton et al., 2005). However, because positioning at the time of taking the scan is very important for DXA, improper positioning could have a significant effect on BMD. Because of the 2D nature of DXA, this imaging method doesn't differentiate between slender bone and fat bone. It characterizes small bone as low BMD and fat bone as high BMD, regardless of the volumetric BMD,

causing inaccuracy in the BMD measured because a slender bone can still have a high BMD and a fat bone can still have a low BMD. Therefore, even though DXA is considered the "gold standard" in diagnosing osteoporosis, it may not be the best tool. Its overlap in BMD, the specific positioning the test requires, and the fact that BMD alone might not be as good at determining fracture risk compared to multiple microstructural parameters, indicate that DXA may not be the most accurate assessment of fracture risk. Other imaging methods have also been explored for osteoporosis risk assessment and are reviewed below.

Once someone has suffered an osteoporotic fracture, conventional radiographs are used to determine the severity and the condition of the bone. Conventional radiographs have limited use in detecting osteoporosis before a fracture occurs, but play a key role in the assessment of fracture status. Osteoporosis can be diagnosed after a fracture by assessing the cause of the fracture. If the cause is classified as minimal impact, such as falling on the hip from a standing position, coughing, or bending over, the fracture is called a fragility fracture. The name "fragility fracture" comes from the low mechanical impact that causes the bone to break. Although BMD can be indirectly assessed from radiography, the variability is high, and most doctors use other methods for their higher accuracy and lower variability.

Quantitative ultrasound (QUS) is an alternative to current radiation-based bone densitometry techniques, like DXA or QCT, and can be performed on peripheral sites, including the calcaneus, tibia, and phalanges. This method is useful in assessing fracture risk and management of osteoporosis. The major advantages of QUS are that it is simple, inexpensive, portable, noninvasive, and radiation-free, which makes this method very useful for osteoporosis screenings (Boehm & Link, 2004). However, the relationship between QUS parameters and fracture is unclear, and the technology, though inexpensive, is still relatively rare clinically.

A more common imaging method is computerized tomography (CT), which produces a 3D image made up of a combination of 2D x-ray images taken from different angles. The combination of images

creates cross-sectional images of different parts of the body. A CT also provides more detailed information than x-rays do. There are several varieties of CT scanners ranging in image resolution and functionality; these include quantitative computerized tomography (QCT), peripheral quantitative computerized tomography (pQCT), and high resolution peripheral quantitative computerized tomography (HR-pQCT). QCT measures BMD using a regular CT scanner that is calibrated to show BMD values. QCT is limited to hospital settings and has the lowest resolution of all the CT scanners. It is not very good at differentiating cortical from trabecular bone. As discussed previously, QCT is often used at the lumbar spine and hip to find BMD. In the peripheral parts of the body, such as the forearms and lower legs, pQCT, a type of QCT, is used to measure BMD. Unlike DXA, which can only measure areal BMD (aBMD), a pQCT scan can measure volumetric BMD (vBMD), along with other measures like stress-strain index and the geometry of the bone. pQCT is more precise, less expensive, and emits less harmful radiation than QCT. HR-pQCT gives a higher resolution picture than pQCT and is considered the gold standard. Although, HR-pQCT scanners are very expensive, and there are very few available for clinical use or research. QCT and pQCT are more appropriate for assessing osteoporotic risk and will be discussed further below.

QCT is the most common clinical CT currently, allowing volumetric measurement of the trabecular interior of bone. Other techniques, like DXA, evaluate a mixture of trabecular and overlying cortical bone. While trabecular and cortical bone can be differentiated using QCT, the trabecular bone is considered the most reliable indicator of overall metabolic integrity, and, therefore, is the best at predicting fracture risk. QCT takes a 3D measurement of the skeletal site. Because of the 3D nature of QCT, osteophytes and soft tissue calcifications do not bias results as much as DXA scans. Although QCT provides high quality and high precision volumetric density measurements, the relatively high amount of radiation exposure can be a problem (Boehm & Link, 2004). QCT is two to three times more sensitive than DXA in detecting BMD loss.

Peripheral QCT (pQCT) measures volumetric BMD in peripheral skeletal sites, such as the distal radius and distal tibia, with a lower dose of radiation and higher image resolution than QCT. pQCT can provide accurate measures of many cross-sectional bone features, including volumetric cortical volumetric bone mineral content (vBMC) and vBMD, trabecular vBMC and vBMD, total bone tissue vBMC and vBMD, cross-sectional cortical bone area, and cross-sectional Cartesian (equatorial) and polar moments of inertia (Schneider, Reiners, Cointry, Capozza, & Ferretti, 2001). QCT measures are expensive, have a higher radiation dose than peripheral measures, and are typically only used in hospital settings. But pQCT scanners are less expensive than QCT and impart less radiation exposure. The radiation exposure that is imparted during a scan is on the peripheral long bone areas of the body, instead of on the organs, which is always preferred in a clinical setting (Sheu et al., 2011**).** pQCT also improves on QCT measures by emitting a more focused x-ray beam to obtain a more detailed image of bone, which allows more specific differentiation between cortical and trabecular bone sites. Although this method is useful in determining BMD of the wrist or ankle, there are limitations on how predictive these values are of femur and spine fractures. There are some studies that have shown correlation between radius and femur parameters and tibia and femur parameters, but there is still a lot of research that needs to be done to determine whether radius or tibia pQCT scans can be predictive of femoral fractures.

Microstructural Parameters Related to Fracture Prediction

As stated earlier, the most accurate prediction of fracture risk is determined from scans of the same area of which fracture risk is trying to be determined, which has been shown in research of femoral fractures (Formica et al., 1998). The combination of BMD measured by DXA and geometry parameters measured by QCT can provide an improved prediction of femoral fracture. For example, in one study, the combination of trabecular BMD of the trochanter and cortical thickness of the neck was most indicative of hip fracture discrimination (Museyko, Bousson, Adams, Laredo, & Engelke, 2015). BMD is

considered a strong independent predictor of hip fracture. Because many femoral fractures occur at the femoral neck, femoral neck parameters alone can accurately predict proximal hip fractures. Femoral neck parameters measured by DXA that have been shown to be associated with fracture prediction are BMD in the trochanteric region, BMD of the neck, femoral neck aBMD, and femoral neck trabecular BMD.

Using pQCT, microstructural parameters of the radius can be determined. Because the distal radius is mainly trabecular bone, trabecular BMD has been shown to be an accurate predictor of Colles' fractures (radial fractures) and hip fractures. This notion is thought to be because both the distal radius and the proximal femur have a large amount of trabecular bone, therefore making them similar metabolically and showing that distal radius microstructural parameters could be correlated to femoral neck microstructural parameters. Trabecular BMD, cortical area, and minimum moment of inertia of the distal radius were all shown to correlate to the same parameters of the femoral neck (Augat, Reeb, & Claes, 1996). Although femoral neck aBMD typically shows the greatest correlation with fracture, cross-sectional moment of inertia, polar moment of inertia, and sectional stress-strain index all show a strong association with fracture. Cross-sectional moment of inertia and sectional stress-strain index appeared to perform better than femoral neck BMD alone, although the differences did not reach statistical significance and, therefore, need more research (Sheu et al., 2011). Other microstructural parameters at the distal radius that have been shown to be correlated to hip fracture prediction include cortical cross-sectional area and total BMC.

Although there have not been many studies on the relationship between parameters of the distal tibia and femoral neck, there are some parameters that have been shown to correlate between the two. Sectional stress-strain index and polar stress-strain index have been shown to have an association with fracture. But again, femoral neck fractures correlated to fracture risk better than tibial parameters did (Sheu et al., 2011). Total BMD of the distal tibia should also be considered when trying to show a correlation between distal tibia parameters and femoral neck parameters.

To date, there are not enough studies showing there is a relationship between microstructural parameters of the distal radius or tibia and microstructural parameters of the femoral neck. If this relationship is proven, a relatively safe pQCT scan could be used to help determine fracture risk before a fall occurs. pQCT determination would be an improvement upon the current DXA and QCT technology by providing maximal information with minimal harm.

This relationship between parameters of the distal radius or tibia and parameters of the femoral neck would allow doctors to use the information provided by a quick pQCT scan at the distal radius or tibia. These pQCT scans, along with traditional DXA scans, could be used to determine if a person is more likely to suffer a hip fracture, leading to limited mobility, surgery, osteoporosis, medication, and reduced quality of life. The pQCT scan they could perform is more specific than DXA, providing additional information to predict fracture to improve early detection and prevention, all while exposing the patient to less radiation than CT. This information could improve prevention of hip fractures by allowing more precise screenings for osteoporosis than DXA. By identifying osteoporosis before a fracture occurs, treatment could be started earlier, potentially preventing a fracture, or the treatment method could be changed to better help the patient prevent fracture.

Building upon previous studies that have been done, this study aims to show that parameters at the hip that can indicate a future hip fracture can be predicted by performing a pQCT scan of the distal radius or tibia, which is easier than other imaging methods and will expose the patient to less radiation. I hypothesize that microstructural parameters related to femoral neck fractures can be estimated by microstructural parameters measured at the distal radius and tibia by pQCT.

Chapter 2

Methods

Subjects

The subjects in this experiment included seven cadavers located at Penn State Berks. Both male and female cadavers of varying ages and causes of death were used (Table 1). The weight of each cadaver was measured using four force plates, one under each corner of the tables the cadavers were on during the dissection process. The weights of just the tables were then taken and these values were subtracted to find the weight of each of the cadavers. From each cadaver, the radius, tibia, and femur were first extracted and stored. All available sets of femora, radii, and tibia were used. The bones were stored in each preserved cadaver body at Penn State Berks. When travelling from Penn State Berks to Penn State University Park with the sets of bones, the moisture was maintained by wrapping the bones in damp paper towels and transporting them in a sealed plastic bag.

pQCT Measurements

The bones were scanned using a pQCT scanner (Stratec XCT 3000, Remeda, Zurich, Switzerland), located in Noll Lab at Penn State University Park. The Stratec software package was used for image processing and the calculation of numerical values. The tibia and radius were aligned to be perpendicular with the scanner. The femoral neck was aligned so that the line from the tip of the head to just below the greater trochanter was perpendicular to the scanner. The femoral head, neck, and trochanteric region were scanned. The head was considered to be at the largest diameter of the head region. The femoral neck was considered to be the thinnest part of the neck region. And the trochanteric

region was scanned so both the greater and lesser trochanters were included in the scan. After the scans were complete, regions of interest were semi-automatically drawn on the image using the Stratec software. See Figure 2 for images of all scan sites.

All measurements of the radius were taken at 33% of the radius length from the distal end. The parameters measured on each radius include cross-sectional moment of inertia (R_CSI), polar moment of inertia (R_PMOI), sectional stress-strain index in the x and y coordinate (R_XSSSI and R_YSSSI, respectively), total bone mineral content (R_totBMC), total bone mineral density (R_totBMD), and trabecular bone mineral density (R_TBMD). All measurements of the tibia were taken at 4% of the tibia length from the distal end. The parameters measured on each tibia include sectional stress-strain index in the x and y coordinate (T_XSSSI and T_YSSSI, respectively), polar stress-strain index (T_PSSI), and total bone mineral density (T_totBMD). And all measurements of the femur were taken at the femoral neck. The parameters measured in the femur include bone mineral density in the trochanteric region (F_BMD.t), bone mineral density in the femoral neck (F_BMD.n), trabecular bone mineral density in the head (F_TBMD.h), trabecular bone mineral density in the trochanteric region (F_TBMD.t), and trabecular bone mineral density in the femoral neck (F_TBMD.n). Each parameter at the femoral neck has been shown to be predictive of femoral neck fractures (Museyko, Bousson, Adams, Laredo, & Engelke, 2015; Kukla et al., 2002).

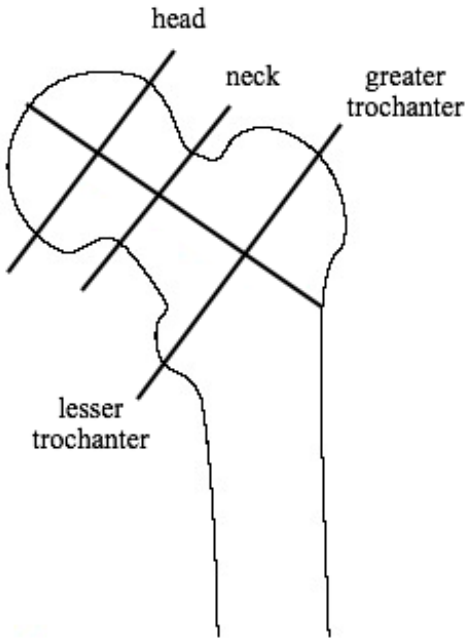

Figure 1. Femoral Neck Percentage Sites

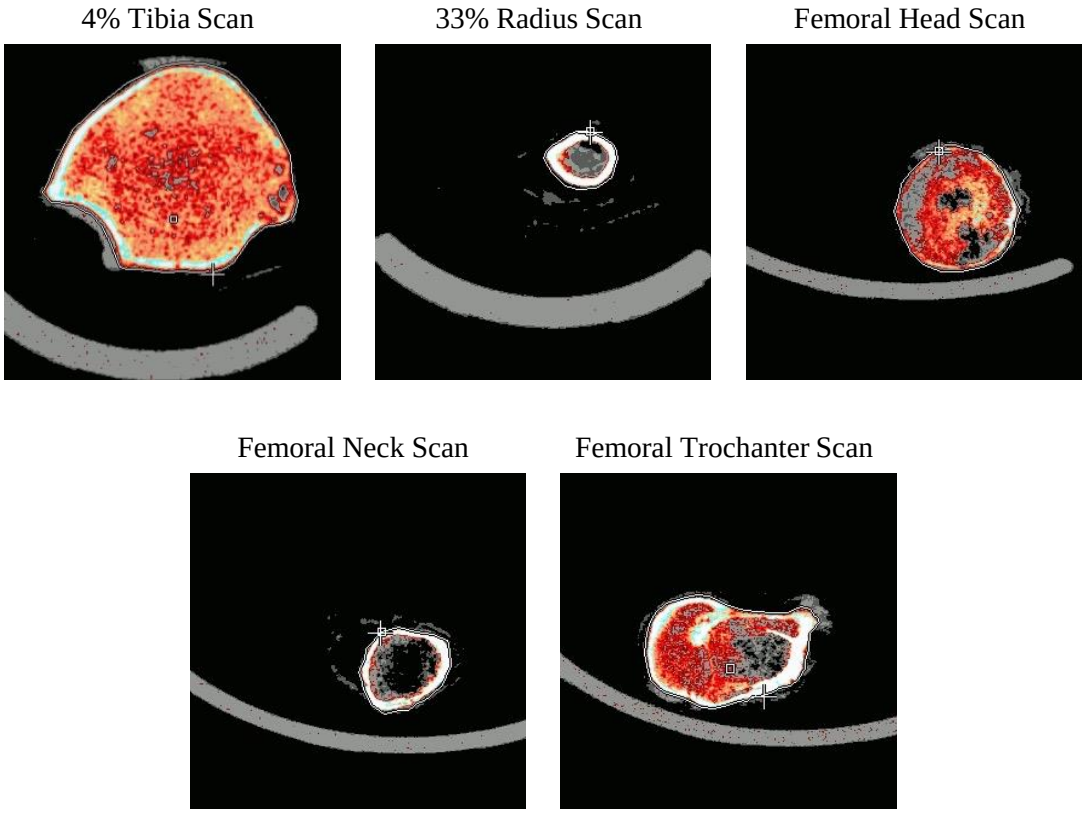

Figure 2. pQCT Image Sites

Statistical Methods

Standard pQCT analysis was done on each bone site to measure microstructural parameters. Data from the analysis was visually checked for normality. All data was analyzed using SPSS for Windows (IBM SPSS Statistics, version 23.0, IBM Corporation, Armonk, NY) statistical software. To determine if measures at the femur are related to measures at the distal radius and tibia, measures at the femur were correlated to measures at the distal radius and the distal tibia. Pearson's correlation coefficient (R-value) were evaluated to determine correlation between the femoral neck microstructural parameters and distal radius microstructural parameters and femoral neck microstructural parameters and distal tibia microstructural parameters. Correlations were statistically significant if the p-value was lower than 0.05. Following correlation, key parameters were entered to perform a regression analysis to see which parameters at the distal tibia alone, distal radius alone, and both the distal radius and distal tibia will best predict fractures of the femoral neck. In order to obtain the most informative prediction model for each of the parameters, entry and removal of variables using a backwards stepwise regression approach was done to enter predictors into the regression equation. The p-value for the entry and removal was 0.05 and 0.10, respectively. To avoid collinearity, all tibia and radius parameter correlations were compared and some were removed. The input into the regression models for all models consisted of R_YSSSI, T_totBMD, R_CSI, R_totBMC, R_totBMD, R_TBMD, T_YSSSI, and T_XSSSI.

Chapter 3

Results

Subjects

The 7 cadavers used in this study were all of varying ages, body mass indexes, and causes of death. Table 1 shows the demographic and anthropometric measures for all cadavers. Although seven cadavers were used, both the right and left sides were used when all bones from both sides were intact, which resulted in nine total sets being used from seven subjects. Five of the cadavers either had a hip arthroplasty or the femur was broken in the removal process, which resulted in only one set from those cadavers. The average age was 78.44 ± 7.28 years. There were four males and three females in the study. The height and mass for the first two subjects below was not available (Table 1). The height of subjects five through seven was measured with a tape measure in the cadaver lab. The average height was 1.64 ± 0.12 meters. The average mass was 71.23 ± 26.63 kg, and the average body mass index was 42.85 ± 14.13 kg/m^2.

Table 1. Cadaver Anthropometric Measurements

Table 1. Demographic and anthropometric measures for each cadaver.

Subject	Gender	Age	Height (m)	Mass (kg)	BMI (kg/m^2)	Cause of Death	Side Used
1	M	68	N/A	N/A	N/A	Amyotrophic lateral sclerosis	R
2	F	93	N/A	N/A	N/A	Cerebrovascular accident	R
3	F	83	1.52	39.76	26.09	Renal failure	L
4	M	71	1.68	61.77	36.85	Chronic myeloid leukemia, myelodysplastic syndrome, graft vs host disease	R
5	M	77	1.80	66.77	37.02	Lung cancer	L
6	F	76	1.52	56.88	37.32	Chronic obstructive pulmonary disease	R and L
7	M	81	1.72	108.26	62.68	Sudden cardiac death	R and L

Parameters

The mean and standard deviation for each parameter are shown in Table 2.

Table 2. Means and Standard Deviations for Parameters

Table 1. Values shown are mean tibial (T_), radial (R_), and femoral (F_) pQCT parameters represented as mean ± standard deviation.

Parameter	Mean ± Standard Deviation
T_PSSI (mm^3)	2181.20 ± 1114.85
T_XSSSI (mm^3)	1173.72 ± 561.67
T_YSSSI (mm^3)	1209.89 ± 632.60
T_totBMD (mg/cm^3)	237.67 ± 75.11
R_CSI (mm^4)	5.28 ± 125.22
R_PMOI (mm^4)	2205.39 ± 1638.31
R_XSSSI (mm^3)	144.33 ± 89.75
R_YSSSI (mm^3)	164.08 ± 106.30
R_totBMC (mg/mm)	95.22 ± 48.47
R_totBMD (mg/cm^3)	763.21 ± 212.76
R_TBMD (mg/cm^3)	163.44 ± 37.49
F_BMD.t (mg/cm^3)	247.87 ± 47.98
F_BMD.n (mg/cm^3)	245.83 ± 26.20
F_TBMD.t (mg/cm^3)	153.70 ± 34.36
F_TBMD.n (mg/cm^3)	169.55 ± 43.31
F_TBMD.h (mg/cm^3)	178.33 ± 54.05

Correlation

Correlations were found between every tibial parameter and femoral parameter and every radial parameter and femoral parameter. Table 3 shows the values of the correlation coefficients for every pair of parameters. Significant correlations were found between F_BMD.t and T_PSSI ($p = 0.015$), T_XSSSI ($p = 0.009$), T_YSSSI ($p = 0.015$), T_totBMD ($p = 0.006$), R_totBMC ($p = 0.025$), and R_totBMD ($p = 0.018$). There were no significant correlations found between F_BMD.n and any of the tibia or radius

parameters. There was a significant correlation found between F_TBMD.t and R_totBMD (p = 0.021). And there were no significant correlations found between F_TBMD.n and all the tibia or radius parameters or between F_TBMD.h and all the tibia or radius parameters. The strongest correlation was found between F_BMD.t and T_totBMD (p = 0.006).

When looking at the same parameters used for both the radius and tibia, the XSSSI for the tibia was 87.7% higher than the XSSSI for the radius. The YSSSI for the tibia was 86.4% higher than the YSSSI for the radius. However, the totBMD for the radius was 68.9% higher than the totBMD for the tibia.

Table 3. Pearson's Correlation Coefficients for Correlations

Table 3. Pearson's correlation coefficients between each set of parameters. * denotes a p-value less than 0.05.

	F_BMD.t	F_BMD.n	F_TBMD.t	F_TBMD.n	F_TBMD.h
T_PSSI	0.770*	0.033	0.349	0.487	0.204
T_XSSSI	0.803*	0.084	0.343	0.512	0.223
T_YSSSI	0.772*	0.047	0.375	0.458	0.164
T_totBMD	0.824*	0.273	0.640	0.187	0.111
R_CSI	0.465	0.654	0.315	0.055	0.228
R_PMOI	0.618	0.115	0.226	0.465	0.278
R_XSSSI	0.602	0.140	0.216	0.442	0.292
R_YSSSI	0.631	0.100	0.221	0.519	0.265
R_totBMC	0.732*	0.059	0.447	0.370	0.044
R_totBMD	0.758*	0.424	0.746*	0.168	0.405
R_TBMD	0.060	0.488	0.265	0.457	0.165

Regression Analysis

Backward regression analysis was used to determine the best models for predicting femoral microstructural parameters from tibial and radial microstructural parameters. The best prediction of F_BMD.t was given by T_XSSSI alone (p = 0.009). The best prediction of F_BMD.n was given by the combination of R_CSI, R_totBMC, and T_YSSSI (p = 0.027). The best prediction of F_TBMD.t was given by the combination of T_totBMD, R_CSI, R_totBMD, R_TBMD, T_YSSSI, and T_XSSSI (p = 0.001). The best prediction of F_TBMD.n was given by the combination of T_totBMD, R_CSI,

R_totBMC, R_totBMD, and T_XSSSI (p = 0.012). And the best prediction of F_TBMD.h was given by the combination of R_CSI, R_totBMC, and T_XSSSI (p = 0.003). All models are shown in Table 4.

Table 4. Best Regression Models for Tibia and Radius Parameters

Table 4. Backward regression models to predict femoral neck parameters from tibia and radius parameters. All models are of significance (p < 0.05).

	R-value	Models
F_BMD.t	0.803	F_BMD.t = 0.069 (T_XSSSI) + 167.327
F_BMD.n	0.904	F_BMD.n = 0.252 (R_CSI) + 1.676 (R_totBMC) – 0.134 (T_YSSSI) + 247.577
F_TBMD.t	1.000	F_TBMD.t = –0.769 (T_totBMD) + 0.140 (R_CSI) + 0.378 (R_totBMD) + 0.801 (R_TBMD) – 0.078 (T_YSSSI) + 0.085 (T_XSSSI) – 88.843
F_TBMD.n	0.988	F_TBMD.n = 1.260 (T_totBMD) + 0.342 (R_CSI) + 4.330 (R_totBMC) – 0.483 (R_totBMD) – 0.427 (T_XSSSI) + 326.041
F_TBMD.h	0.965	F_TBMD.h = 0.464 (R_CSI) + 3.792 (R_totBMC) – 0.361 (T_XSSSI) + 238.097

The best model for F_BMD.t from tibia parameters only was given by T_totBMD alone (p = 0.006). There were no other significant models to predict F_BMD.n, F_TBMD.t, F_TBMD.n, or F_TBMD.h from tibia parameters alone. All models are shown in Table 5.

Table 5. Best Regression Models for Tibia Parameters

Table 5. Backward regression models to predict femoral neck parameters from tibia parameters. All models are of significance (p < 0.05).

	R-value	Models
F_BMD.t	0.824	F_BMD.t = 0.526 (T_totBMD) + 122.736
F_BMD.n	N/A	No significant models
F_TBMD.t	N/A	No significant models
F_TBMD.n	N/A	No significant models
F_TBMD.h	N/A	No significant models

The best model to predict F_BMD.t from radius parameters only was given by the combination of R_CSI, R_PMOI, R_XSSSI, R_YSSSI, and R_TBMD (p = 0.037). The best model to predict F_BMD.n from radius parameters was given by the combination of R_PMOI, R_XSSSI, R_totBMC, R_totBMD, and R_TBMD (p = 0.015). The best model to predict F_TBMD.t by solely radius parameters was given

by the combination of R_PMOI, R_XSSSI, R_YSSSI, R_totBMD, and R_TBMD (p = 0.001). The best model to predict F_TBMD.n from solely radius parameters was given by the combination of R_CSI, R_YSSSI, R_totBMC, and R_totBMD (0.047). And the best model to predict F_TBMD.h from only radius parameters was given by the combination of R_XSSSI and R_totBMC (p = 0.012). All models are shown in Table 6.

Table 6. Best Regression Models for Radius Parameters

Table 6. Backward regression models to predict femoral neck parameters from tibia parameters. All models are of significance (p < 0.05).

	R-value	Radius Parameters Only
F_BMD.t	0.974	F_BMD.t = 0.382 (R_CSI) – 0.551 (R_PMOI) + 3.634 (R_XSSSI) + 5.699 (R_YSSSI) + 1.106 (R_TBMD) – 180.033
F_BMD.n	0.997	F_BMD.n = 0.445 (R_PMOI) – 3.142 (R_XSSSI) – 3.141 (R_totBMC) + 0.377 (R_totBMD) – 0.553 (R_TBMD) + 360.378
F_TBMD.t	0.998	F_TBMD.t = 0.160 (R_PMOI) – 2.455 (R_XSSSI) – 0.572 (R_YSSSI) + 0.198 (R_totBMD) + 0.442 (R_TBMD) + 24.545
F_TBMD.n	0.932	F_TBMD.n = –0.127 (R_CSI) – 2.341 (R_YSSSI) + 5.908 (R_totBMC) – 0.383 (R_totBMD) + 284.350
F_TBMD.h	0.877	F_TBMD.h = –1.858 (R_XSSSI) + 3.248 (R_totBMC) + 137.128

Chapter 4

Discussion and Conclusion

The purpose of this study was to show that microstructural parameters at the femoral neck that are related to femoral neck fractures can be predicted by microstructural parameters at the distal radius and distal tibia. The results have been shown by numerous regression models (tables 4, 5, and 6). All statistically significant models were of strong to very strong correlation strength (R = 0.803 to R = 1.000). All models, except for the model for F_BMD.t, resulted from a combination of both tibia and radius parameters. F_BMD.t was predicted by just T_XSSSI, showing the importance of parameters from another weight bearing bone in predicting femoral neck fracture risk. Both models for F_TBMD.t had a correlation value of 1.000, meaning the model perfectly fits the data. This is an excellent value for the low number of cadavers used in this study. Both models include a combination of radial and tibial mechanical strength indicators and compositional parameters. This extremely high correlation coefficient shows the importance of both radius and tibia parameters and a variety of different parameters in determining trabecular BMD in the femoral trochanter region.

All tibia and radius parameters were correlated to all the femoral neck parameters. In general, tibia parameters showed more correlation to femoral parameters than radius parameters. Tibia parameters were shown to be only statistically correlated to trochanter BMD. Only radius compositional parameters were significantly correlated to femoral trochanter BMD and trabecular BMD. The rest of the parameters correlated to F_BMD.t were of moderate strength correlation. Almost all of the tibia and radius parameters correlated to the four other femoral neck parameters were of weak to low strength. No tibia or radius parameters were statistically correlated to F_BMD.n, F_TBMD.n, or F_TBMD.h. This information shows that distal tibia and radius parameters are more strongly correlated to the trochanter region of the femur, and not as related to femoral neck or head parameters. No single tibia parameters were predictive

of femoral neck parameters, but tibia parameters were significant in determining models for other femoral neck parameters other than trochanter BMD.

In general, tibial and radial parameters that were the same seem to be highly correlated to each other. For example, tibia XSSSI and radius XSSSI are highly correlated to each other (see Appendix A). Mean total BMD in the femoral neck (M = 245.83 mg/cm^3) and in the trochanter region (M = 247.87 mg/cm^3) was much closer in value to the mean R_totBMD as compared to the T_totBMD. This is interesting because a greater number of tibia parameters were more highly correlated to trochanter parameters than radius parameters were.

One previous study performed by Sheu et al., 2011, compared tibia microstructural parameters with fracture risk found that XSSSI, YSSSI, and PSSI were all correlated to femoral neck fracture risk, which was similar to what was found in the current study. In the current study, XSSSI, YSSSI, and PSSI were all shown to be strongly correlated to F_BMD.t ($R = 0.803$, $R = 0.772$, and $R = 0.770$, respectively), but very weakly related to F_BMD.n ($R = 0.084$, $R = 0.047$, and $R = 0.033$, respectively). All of the mechanical strength indicators of the tibia used are significantly related to trochanteric BMD, which shows the possibility of tibia parameters' ability to predict trochanter fractures, but maybe not as many femoral neck fractures. One model to predict F_BMD.t from only tibia parameters ($R = 0.860$, $p < 0.05$) used both T_XSSSI and T_totBMD. Another model ($R = 0.824$, $p < 0.01$) used only T_totBMD to predict F_BMD.t. Another model, using both radius and tibia parameters as an input, gave a model ($R = 0.803$, $p < 0.01$) solely using T_XSSSI to predict F_BMD.t, which again shows the importance of using the distal tibia site as a reliable way to predict fracture risk in the trochanteric region. There were no other models for other femoral parameters that were of significant value using just tibia parameters, showing that tibia parameters are particularly important in determining BMD in the trochanter region. The tibia, like the femur, is a weight bearing bone, which could explain why the tibia and femoral trochanter region were highly correlated and why the models for this region were exceedingly strong. However, the lack of significant models for the other femoral parameters using just tibia parameters shows that radius

parameters are critical to creating significant, meaningful models to predict a variety of femoral region parameters.

In this study, one model found for F_BMD.n ($R = 0.997$, $p < 0.05$) also showed that a similar combination, involving PMOI, XSSSI, totBMC, totBMD, and TBMD, was strongly correlated to F_BMD.n. The combination was similar to a previous study performed by Sheu et al., 2011. Because it has been shown that F_BMD.n is a strong predictor of femoral neck fractures, this model is a good representation of femoral neck fracture risk. However, TBMD of the distal radius was not shown to be highly correlated with F_BMD.n ($R = 0.488$, $p > 0.05$), which contradicts what another study has previously shown (Augat, Reeb, & Claes, 1996). This weak correlation was surprising because of the similarity in the amount of trabecular bone between the femoral neck and distal radius. However, there was no single radial or tibial parameter that was significantly correlated to TBMD, which could be explained by the limitations of this study.

The first major limitation to this study was the low sample size. There were only seven cadavers, with either one side or two sides of the body used, making a total number of nine sets. Despite the small number of cadavers used, very high correlations were found, demonstrating this study's significance. Another limitation is the causes of death of the subjects. Most of the cadavers seemed to be bed bound for quite some time before they died, which was determined by the level of atrophy to the legs and the higher BMIs observed. The cadavers could have BMDs much lower than the average moderately healthy person. Therefore, it may not be fair to extrapolate from these models to the general population. The study needs to be repeated on a younger population who are more physically active and have no medical problems. Because pQCT is not designed to be used on cadaver limbs, another challenge arose during imaging processing. However, pQCT in a live, at risk population would be beneficial because it is quick, accurate, and emits low radiation. The use of pQCT, while vital to this study, could have been upgraded to a higher quality imaging method, such as HRpQCT. pQCT was chosen over this option because it costs less, is

more clinically available, has lower radiation, and is quicker than some of the more accurate imaging methods.

Despite all the limitations involved with this study, it was the first to compare distal tibia and distal radius microstructural parameters to femoral neck parameters using pQCT for all bones. And even with the multiple limitations, the models found in this study were very highly to perfectly (R = 1.000) correlated between tibia and radius parameters and femoral neck parameters. There have been multiple studies comparing just distal radius parameters to femoral scans from different imaging methods, including DXA or pQCT (Formica et al., 1998 and Augat et al., 1996). But this is the first study to use pQCT to measure femoral microstructural parameters from the femoral head and trochanteric region. This is also the first study to compare pQCT scans of the distal tibia, a weight-bearing bone unlike the radius, to different femoral neck sites. This study has shown the accuracy in predicting femoral parameters by using a combination of radius and tibia parameters, as opposed to just one or the other.

In this study, microstructural parameters of the distal tibia and distal radius were able to strongly predict femoral neck microstructural parameters, as measured by pQCT. The study demonstrated that pQCT measures at the distal tibia or distal radius could be used to calculate femoral neck fracture risk. By using pQCT, along with other imaging modalities, radiologists could get more accurate measurements than from DXA alone, with less harmful radiation than CT.

Hip fractures are a huge problem for both individual patients and the health care system as a whole. By using a quick pQCT scan of the radius or tibia, along with traditional DXA scans, earlier detection and prevention of osteoporosis-related fractures could be improved. If osteoporosis is accurately diagnosed by pQCT before a fracture occurs, fracture could be prevented by starting medical interventions earlier in the osteoporosis process, which could improve the person's mobility and quality of life, all while reducing the costs to the person and medical industry.

Appendix A

Collinearity Table

	T_PSSI	T_XSSSI	T_YSSSI	T_totBMD	R_CSI	R_PMOI	R_XSSSI	R_YSSSI	R_totBMC	R_totBMD	R_TBMD
T_PSSI	1.000	.993	.998	.764	.224	.965	.958	.961	.966	.656	.047
T_XSSSI	.993	1.000	.989	.795	.298	.934	.928	.930	.942	.660	.017
T_YSSSI	.998	.989	1.000	.762	.246	.959	.950	.955	.967	.662	.053
T_totBMD	.764	.795	.762	1.000	.259	.649	.674	.638	.807	.900	.084
R_CSI	.224	.298	.246	.259	1.00	.000	-.038	-.010	.080	.144	-.179
R_PMOI	.965	.934	.959	.649	.000	1.000	.997	.996	.957	.569	.079
R_XSSSI	.958	.928	.950	.674	.038	.997	1.000	.990	.959	.582	.097
R_YSSSI	.961	.930	.955	.638	.010	.996	.990	1.000	.956	.584	.016
R_totBMC	.966	.942	.967	.807	.080	.957	.959	.956	1.000	.775	.037
R_totBMD	.656	.660	.662	.900	.144	.569	.582	.584	.775	1.000	-.138
R_TBMD	.047	.017	.053	.084	.179	.079	.097	.016	.037	-.138	1.000

Appendix B

All Significant Models for Femoral Neck Parameters

	Both Tibia and Radius Parameters
F_BMD.t	**Model 1:** p = 0.033, R = 0.976 F_BMD.t = –0.833 (T_totBMD) – 2.400 (R_totBMC) + 0.464 (R_totBMD) + 0.636 (R_TBMD) + 0.235 (T_XSSSI) – 60.104 **Model 2:** p = 0.042, R = 0.936 F_BMD.t = –1.367 (R_totBMC) + 0.187 (R_totBMD) + 0.255 (R_TBMD) + 0.133 (T_XSSSI) + 37.916 **Model 3:** p = 0.019, R = 0.917 F_BMD.t = –1.198 (R_totBMC) + 0.165 (R_totBMD) + 0.125 (T_XSSSI) + 89.752 **Model 4:** p = 0.018, R = 0.858 F_BMD.t = 0.091 (R_totBMD) + 0.046 (T_XSSSI) + 124.684 **Model 5**: p = 0.009, R = 0.803 F_BMD.t = 0.069 (T_XSSSI) + 167.327
F_BMD.n	**Model 1:** p = 0.027, R = 0.904 F_BMD.n = 0.252 (R_CSI) + 1.676 (R_totBMC) – 0.134 (T_YSSSI) + 247.577
F_TBMD.t	**Model 1:** p = 0.036, R = 1.000 F_TBMD.t = –0.769 (T_totBMD) + 0.140 (R_CSI) – 0.003 (R_totBMC) + 0.378 (R_totBMD) + 0.801 (R_TBMD) – 0.077 (T_YSSSI) + 0.084 (T_XSSSI) – 88.863 **Model 2:** p = 0.001, R = 1.000 F_TBMD.t = –0.769 (T_totBMD) + 0.140 (R_CSI) + 0.378 (R_totBMD) + 0.801 (R_TBMD) – 0.078 (T_YSSSI) + 0.085 (T_XSSSI) – 88.843
F_TBMD.n	**Model 1:** p = 0.012, R = 0.988 F_TBMD.n = 1.260 (T_totBMD) + 0.342 (R_CSI) + 4.330 (R_totBMC) – 0.483 (R_totBMD) – 0.427 (T_XSSSI) + 326.041
F_TBMD.h	**Model 1:** p = 0.023, R = 0.982 F_TBMD.h = –0.138 (T_totBMD) + 0.395 (R_CSI) + 2.810 (R_totBMC) + 0.130 (R_totBMD) – 0.294 (T_XSSSI) + 187.538 **Model 2:** p = 0.004, R = 0.980 F_TBMD.h = 0.406 (R_CSI) + 3.016 (R_totBMC) + 0.085 (R_totBMD) – 0.315 (T_XSSSI) + 193.698 **Model 3:** p = 0.003, R = 0.965 F_TBMD.h = 0.464 (R_CSI) + 3.792 (R_totBMC) – 0.361 (T_XSSSI) + 238.097

	Tibia Parameters Only
F_BMD.t	**Model 1:** p = 0.018, R = 0.860 F_BMD.t = 0.034 (T_XSSSI) + 0.322 (T_totBMD) + 130.952 **Model 2:** p = 0.006, R = 0.824 F_BMD.t = 0.526 (T_totBMD) + 122.736
F_BMD.n	No significant models
F_TBMD.t	No significant models
F_TBMD.n	No significant models
F_TBMD.h	No significant models

	Radius Parameters Only
F_BMD.t	**Model 1:** p = 0.037, R = 0.974 F_BMD.t = 0.382 (R_CSI) – 0.551 (R_PMOI) + 3.634 (R_XSSSI) + 5.699 (R_YSSSI) + 1.106 (R_TBMD) – 180.033
F_BMD.n	**Model 1:** p = 0.015, R = 0.997 F_BMD.n = 0.445 (R_PMOI) – 3.142 (R_XSSSI) – 3.141 (R_totBMC) + 0.377 (R_totBMD) – 0.553 (R_TBMD) + 360.378
F_TBMD.t	**Model 1:** p = 0.004, R = 0.999 F_TBMD.t = –0.27 (R_CSI) + 0.204 (RPMOI) – 2.844 (R_XSSSI) – 0.922 (R_YSSSI) + 0.207 (R_totBMD) + 0.390 (R_TBMD) = 44.516 **Model 2:** p = 0.001, R = 0.998 F_TBMD.t = 0.160 (R_PMOI) – 2.455 (R_XSSSI) – 0.572 (R_YSSSI) + 0.198 (R_totBMD) + 0.442 (R_TBMD) + 24.545
F_TBMD.n	**Model 1:** p = 0.047, R = 0.932 F_TBMD.n = –0.127 (R_CSI) – 2.341 (R_YSSSI) + 5.908 (R_totBMC) – 0.383 (R_totBMD) + 284.350
F_TBMD.h	**Model 1:** p = 0.039, R = 0.887 F_TBMD.h = –0.062 (R_CSI) – 1.979 (R_XSSSI) + 3.486 (R_totBMC) + 133.250 **Model 2:** p = 0.012, R = 0.877 F_TBMD.h = –1.858 (R_XSSSI) + 3.248 (R_totBMC) + 137.128

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