REVIEW

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Cortical Bone Assessed With Clinical Computed Tomography at the Proximal Femur

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ABSTRACT

Hip fractures are the most serious of all fragility fractures in older people of both sexes. Trips, stumbles, and falls result in fractures of the femoral neck or trochanter, and the incidence of these two common fractures is increasing worldwide as populations age. Although clinical risk factors and chance are important in causation, the ability of a femur to resist fracture also depends on the size and spatial distribution of the bone, its intrinsic material properties, and the loads applied. Over the past two decades, clinical quantitative computed tomography (QCT) studies of living volunteers have provided insight into how the femur changes with advancing age to leave older men and women at increased risk of hip fractures. In this review, we focus on patterns of cortical bone loss associated with hip fracture, age-related changes in cortical bone, and the effects of drugs used to treat osteoporosis. There are several methodologies available to measure cortical bone in vivo using QCT. Most techniques quantify bone density (g/cm^3), mass (g), and thickness (mm) in selected, predefined or "traditional" regions of interest such as the "femoral neck" or "total hip" region. A recent alternative approach termed "computational anatomy," uses parametric methods to identify systematic differences, before displaying statistically significant regions as color-scaled maps of density, mass, or thickness on or within a representative femur model. This review will highlight discoveries made using both traditional and computational anatomy methods, focusing on cortical bone of the proximal femur. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: CORTICAL BONE; QUANTITATIVE COMPUTED TOMOGRAPHY; HIP FRACTURE; OSTEOPOROTIC DRUGS; AGING

Introduction

Hip fractures are the most serious of all fragility fractures, leading to significant reductions in mobility, independence, quality of life, and increased mortality in older people of both sexes.[1] Fractures of the proximal femur are projected to occur worldwide in more than 6.3 million people per year by 2050.[2] Hip fractures (which are split approximately 50:50 into cervical and trochanteric types[3]) result from a structural failure of the femur that is likely initiated at the material level, whereby the load applied to the bone exceeds its load-bearing capacity. A trip, stumble, or fall is the cause of more than 90% of hip fractures, but a minority occur spontaneously in stance.[4] Whether a femur fractures under these loads depends on the size and spatial distribution of bone, its intrinsic material properties and also factors that contribute to the loads applied. Cortical bone is key to the structural stability of whole bone, but it is important to remember that skeletal structure is only one component of fragility fracture risk, with clinical risk factors and chance also playing major roles.

This review highlights discoveries made by researchers studying individuals who have undergone clinical computed tomography (CT) of the pelvis and hips, focusing on cortical bone of the proximal femur and patterns of bone loss associated with hip fracture. We also discuss important discoveries made using clinical CT in trials and aging cohorts, including age-related changes in cortical bone and the effects of drugs used to treat osteoporosis. An important justification for undertaking this review has been the growing consensus that studying the determinants of specific hip fracture types in three dimensions (principally cervical versus trochanteric) will improve our understanding of fracture causation, prevention, and mechanics.[5] The current clinical standard for fracture prediction is dual-energy X-ray absorptiometry (DXA) of the femoral neck, but DXA measures two-dimensional bone "density"—an amalgam of cortical and trabecular bone density, structure, and bone size. Three-dimensional (3D) imaging modalities such as quantitative CT (QCT) can measure cortical and trabecular compartments separately, regions that may play independent roles in fragility fracture. 3D QCT can also be reformatted or projected to give "DXA-like" two-dimensional areal bone mineral density (aBMD) measures. In fact, either DXA femoral neck aBMD or hip QCT measures of the same region can now be entered into the WHO absolute

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Table 1. Summary of Study Design and Technical Parameters in the QCT Studies at the Proximal Femur

Population	Study design	Total (*n*)	Sex	Age (years)	Pixel size (mm)	ST (mm)	Phantom	CT manufacturer and scanner[a] (kVp; target mAs)	Kernel	Tool	References
Icelandic (AGES-Reykjavik)	Cross-sectional (age)	1715	F/M	67–93	0.977	1	Image Analysis	Siemens Sensation (120; 140)	Standard	Fig. 1*D*	(53)
	Cross-sectional (age)	107		65–90						See Carpenter and colleagues[67]	(67)
	Prospective case-control	441		average 79.5						Fig. 1*B*	(48)
	Longitudinal	400		66–90						Fig. 1*B*	(54)
U.S. (Rochester residents)	Cross-sectional (age)	696	F/M	20–97	0.74	2.5	Mindways	GE Light Speed QX/i (120; 100)	Standard	See Camp and colleagues[39]	(52)
	Cross-sectional (age)	358	F							Fig. 1*A*	(65)
U.S. (MrOS)	Cross-sectional (age)	3358	M	65–100	0.94	3	Image Analysis	GE ProSpeed, GE HiSpeed Advantage	N/A	Fig. 1*D*	(66)
	Cross-sectional (race)	3305						Philips MX8000, Phillips CT-Twin			(70)
	Prospective (hip fracture)	3347						Siemens Somatom Plus 4			(45)
	Prospective case-cohort (hip fracture)	250						Toshiba Aquilion; Picker PQ-5000 (80; 280)		Fig. 1*C*	(46)
Chinese	Case-control	111	F	≥65	0.88	3	Image Analysis	GE CT Pro FII (120; 200)	N/A	Fig. 1*D*	(25)
	Case-control	75								Fig. 1*E*	(30)
Japanese	Case-control	72	F	68–83	0.625/0.65	0.5	Fujirebio	Toshiba Aquilion 16; Siemens Somatom Cardiac 64 (120; 250)	N/A	Fig. 1*B*	(26)
N/A (HORIZON subset, controls)	Cross-sectional	27	F	65–86	0.94	3	Image Analysis	N/A (80; 280)		Fig. 1*C*	(34)
British	Cross-sectional (age)	100	F	20–90	0.59	1	Mindways	Siemens Somatom 64 Sensation (120; 160)	B20f	Fig. 1*B*	(31)
Czech	Case-control	150	F	average 76.6	N/A	≤1	Siemens	Siemens Sensation 40/16 (N/A; N/A)	B10/20	Fig. 1*F*	(43)
Japanese	Longitudinal	59	F	54–84	0.625	0.5	Fujirebio	Toshiba Aquilion 16 (120; 250)	N/A	Fig. 1*B*	(64)
N/A	Case-control	100	F	55–89	0.74	0.625	Mindways	GE LightSpeed 64 VCT (120; 170–200)	Bone plus	Fig. 1*C*	(47)
U.S. (Rochester residents) and Icelandic (AGES-Reykjavik)	Cross-sectional (age)	349	F	21–97	0.74	2.5	Mindways	GE LightSpeed QX/i (120; 100)	Standard	Fig. 1*E*	(35,44)
	Prospective case-control	222	F	average 79	0.977	1	Image Analysis	Siemens Sensation (120; 140)	Standard		
French and British	Case-control	107	F	≥60	0.29[b]	1/1.25	Siemens; Mindways	Siemens Somatom Volume Zoom 4; GE LightSpeed 16 (120; 170)	B40s; standard	Fig. 1*A*	(50)
U.S.	PTH, ALD; Drug study	178	F	55–85	0.78–0.94	3	Image Analysis	N/A (3 centers) (80; 280)	N/A	Fig. 1*D*; see Keaveny and colleagues[83]	(75,76,83)
N/A	TPTD, ALD; Drug study	56	F	45–85	N/A	N/A	N/A	N/A (7 centers) (N/A; N/A)	N/A	Fig. 1*B*	(77)
U.S., British, Chinese, Argentine, Canadian (subset from HORIZON)	ZOL; drug study	179	F	average 74.2	0.94–0.97	3	Image Analysis	GE LightSpeed; GE HiSpeed Advantage; Siemens Somatom 16; Picker PQ5000, Toshiba XpressGx (80; 280)	N/A	Fig. 1*D*	(78,79)

U.S.	IB; drug study	93	F	55–80	0.39[b]	1	Mindways	N/A (13 centers) (120; 170)	Medium body	Fig. 1*A*	(80,81)
Japanese	ELD/ALF; drug study	193	F/M	52–85	0.5/0.625	1/1.25	Fujirebio	Toshiba Aquilion 4/16/64; GE-Yokogawa LightSpeed Ultra 4/8/16; Siemens Somatom Volume Zoom (Plus 4) (120–140; 200–300)	FC30 Bone; B80	Fig. 1*B*	(82)
German and Spanish (subset from EUROFORS)	TPTD; drug study	52	F	≥55	N/A	3	Mindways	Siemens Somatom 16/Volume Zoom; GE LightSpeed 16; Toshiba Asteion (120; 70–200)	N/A	Fig. 1*B*	(84)
Subset from FREEDOM	Denosumab	209	F	60–90	0.78	≤1.25	Mindways	GE, Philips, Siemens, Toshiba (120; 170)	Medium	Fig. 1*B*	(85)
	Drug study	62								Fig. 1*A*	(87)
6 European countries (subset from OCEAN)	Odanacatib, ALD; drug study	123	F	55–75	0.4	1/1.25	Mindways	GE, Philips, Toshiba, Hitachi, Siemens (9 scanners); (120; 170)	Medium	Fig. 1*A*	(90)
7 countries	Odanacatib; drug study	218	F	45–85	0.39	1/1.25	Mindways	N/A (13 centers) (120; 170)	Medium	Fig. 1*B*	(89)

ST = slice thickness; AGES-Reykjavik = Age Gene/Environment Susceptibility-Reykjavik; F = female; M = male; MrOS = Osteoporotic Fractures in Men; N/A = not available; PTH = parathyroid hormone; ALD = alendronate; TPTD = teriparatide; ZOL = zolendronate; IB = ibendronate; ELD = eldecalcitol; ALF = alfacalcidol; EUROFORS = European Study of Forsteo; FREEDOM = Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease; OCEAN = ONO-5334 cathepsin K inhibitor European.

[a]Scanner details apply across the whole study population and not to specific study designs.

[b]Pixel size calculated assuming reconstruction matrix of 512 × 512.

fracture risk calculator for adults, Fracture Risk Assessment Tool (FRAX™).

Acquisition of Clinical CT Images For Hip Measurements

CT scanners produce a series of thin "tomograms" or axial slices through the body region of interest (ROI), for our purposes the pelvis and hips. A position statement from experts in clinical QCT has reviewed the clinical application of hip and spine CT technology in detail.[6] Despite this International Society for Clinical Densitometry (ICSD) consensus document, there is no "one size fits all" approach to clinical CT measurements. Table 1 shows the considerable variation in the numerous parameters reported when acquiring the CT images for various clinical studies. Not only will the acquisition parameters set by the CT radiographer team influence the quality of the images attained, but so will routine dose-limiting of the imaging system. As an example of the dose involved for multislice hip CT, acquiring an image slice thickness of 1 mm will involve an approximate typical effective dose of 3 mSV in comparison to 0.05 mSV for a DXA acquisition, a factor which must be borne in mind when contemplating QCT in clinical practice.[7] Scan protocol variables such as patient positioning, X-ray tube peak voltage (kVp), tube current, pitch, gantry rotation speed, detector configuration, table height, and reconstruction algorithm will all affect measurements. Indeed, a study using ex vivo spine specimens to simulate patient repositioning found that BMD QCT precision was 1.4% using the same scan protocol, 1.8% when permitting some variation in the X-ray tube current and table speed. However, without any constraints on the clinical QCT protocol the precision fell to 3.6% at worst.[8] Although variations in kVp and table height can be controlled when measuring bone density (by using a calibration phantom that is accurately positioned in the field of view[9]), further studies are needed to better characterize potential sources of variation in measurements, not least to help in the interpretation of multicenter studies. For an in-depth analysis of the technical aspects of skeletal QCT measurements, we refer readers to a recent book chapter that covers the physics in detail.[10]

Cortical Bone

Human bone is composed of two fundamental compartments: cortical bone and trabecular bone.[11,12] Cortical bone makes up approximately 80% of the skeletal mass of an adult human[13] and is primarily found in the shaft of long bones formed as a shell around the trabecular bone. It can withstand much greater load than trabecular bone and deforms little before failure. In contrast, trabecular bone can deform significantly but will fail at a much lower load. Even though trabecular bone cannot withstand high loading, it is important for stiffening the structure by holding together the shell, preventing buckling, supporting cortical bone in the case of impact loads and distributing loads at extremities. Trying to discern the relative contributions of hip cortical and trabecular bone to load bearing during locomotion and falling using cadaveric specimens in the laboratory has been challenging.[14–19] Differing results may to some extent reflect the fact that cortical and trabecular bone structure is affected by age and the severity of osteoporosis, with a large variation between individuals. There are also considerable challenges in replicating bipedal gait and hip fracture in the laboratory as well

as differences in the methods applied. Simulations involving cadaveric hip specimens suggest that fractures involve stereotypical locations of the femoral cortex due to excessive focal load concentration.[16,19,20]

Trabecular bone is also critical to hip fracture susceptibility, with specific methods existing for the analysis of femoral trabecular bone in vivo.[21] Because trabecular bone remodels faster than cortical bone, the earliest effects of osteoporotic medications are often seen in this compartment. Although we concentrate on cortical bone in this review, it is important to remember that trabecular density measured in the proximal femur is often a necessary inclusion in multivariate models predicting hip fracture or discriminating fracture from controls. Accurate measurement of femoral microstructure (including cortical porosity and trabecular parameters) requires much greater resolution than is possible with clinical CT; however, it may still be highly relevant to age-related changes and hip fragility.[22] Relevant discoveries on the role of bone microstructure have been reviewed in detail recently.[23]

Summary of CT Image Analysis Techniques For the Hip

Several image analysis techniques can be used to reconstruct and then subdivide the 3D femoral structure, permitting measurements of density (g/cm^3), mass (g), thickness (mm), area (cm^2), and volume (cm^3) in cortical and trabecular compartments of selected ROIs (traditionally the ROIs featured in Fig. 1*A*). The most common are the "femoral neck" (FN), "trochanteric" (TR), and "total hip," similar to those used in DXA. Several techniques further subdivide these tubular ROIs into anatomical quadrants. Commercial and noncommercial programs are available to measure cortical bone in vivo:[24–35] we discuss the studies reporting on these measurements. Figure 1 shows the anatomical locations of measurements reported by different researchers. There are challenges in measuring all of these variables from clinical CT, chiefly relating to the phenomenon of partial volume averaging at low in vivo resolution, which makes delineating cortical and trabecular bone into definite compartments challenging. All the techniques featured in this review have been published in peer-reviewed literature,[10,27–29,31–34,36–41] and some of the technical limitations common to all the methods are described at the end of this review.

An alternative approach to measuring traditional ROIs is to consider the full spatial distribution of values among all subjects through the process of statistical parametric mapping (SPM) to identify new 3D ROIs where subjects, on average, differ from controls.[42] This methodology has been termed "computational anatomy," and encompasses techniques known as voxel-based morphometry (VBM) for mapping 3D density values (Fig. 1*E*), tensor-based morphometry (TBM), and cortical bone mapping (CBM) (Fig. 1*F*) for mapping 3D cortical thickness and mass.[30,35,43,44]

QCT and Hip Fracture

Many studies have investigated cortical bone in the hip and its association with hip fracture risk, providing useful information concerning causation of hip fracture, the evaluation of hip fracture risk, and potential targets for therapeutic and exercise intervention. All studies have shown that cortical measurements are associated with hip fracture, and some, but not all, have reported that cortical measurements predict hip fracture independently of aBMD by DXA. These studies differ in the number of participants, study design, whether fractures were classified into femoral neck or trochanteric (thought to be of critical importance[3]), as well as how and where in the hip cortical bone was measured. Generally, neither the cases nor the controls have been optimally selected in the studies comparing patients with *existing* hip fracture with controls. Cases are problematic because the inevitable surgical repair of a hip fracture leaves a CT image with streaking metalwork artifact on the contralateral "good" hip, requiring instead a technically challenging preoperative study in a patient with acutely painful hip fracture. Not only that, but the studies of patients with existing hip fracture (awaiting surgical fixation) inevitably involves an assumption whereby the "good hip" is uses as a surrogate for the fractured hip. Higher resolution scanning of controls is also problematic because the dose associated with pelvic or hip CT (sometimes involving the gonads) would need to be justified, meaning that controls may be selected from "healthy" individuals who are having CT for other reasons. Only two studies, Osteoporotic Fractures in Men (MrOS) in American (men only) and the Age Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) study (both sexes), are truly prospective because the cohorts were assembled and imaged many years prior to fracture. Crucially, none of the studies have reported that cortical measurements predict fracture significantly better than femoral neck DXA aBMD values. This is not surprising because aBMD by DXA is an amalgam measure that encompasses elements of trabecular and cortical bone, including cortical structure and overall bone size.

In studying Chinese women with and without hip fracture with clinical CT, Cheng and colleagues[25] estimated cortical density and volume in the femoral neck, trochanteric, and total hip regions, as well as the average cortical thickness in the femoral neck (Fig. 1*D*). All these cortical variables discriminated between the 45 fracture cases and 66 younger controls; however, trabecular density discriminated cases from controls better than cortical density. Average cortical thickness in the femoral neck made an independent contribution to discriminating fractures from controls in a model including trabecular density, but did not when the models included total hip DXA aBMD.

Using the same ROIs (Fig. 1*D*), the association of QCT variables with hip fracture was explored in a prospective study of older American men from the MrOS study (3347 men among whom 42 sustained hip fractures during follow-up, age $\geq$65 years).[45] Significant predictors of hip fracture were similar to those of Cheng and colleagues[25]: cortical density in the femoral neck was a determinant of fracture, as was cortical volume and the percentage cortical volume (of total hip volume) when adjusted for age, body mass index (BMI) and trial center. Independent predictors of hip fracture risk were lower percent cortical volume, smaller bone size (as femoral neck cross-sectional area [CSA]), and lower trabecular density of the femoral neck. In contrast to Cheng and colleagues,[25] percent cortical volume and bone size continued to make independent contributions after adjustment for DXA aBMD. Nevertheless, overall fracture prediction was not improved compared with DXA alone.

Yang and colleagues[46] used a different approach to perform a QCT case-cohort study using the same men (cohort $n = 210$, cases $n = 40$). They calculated cortical, trabecular, and integral density as well as cortical thickness in four quadrants of cross-sections along the entire length of the femoral neck,

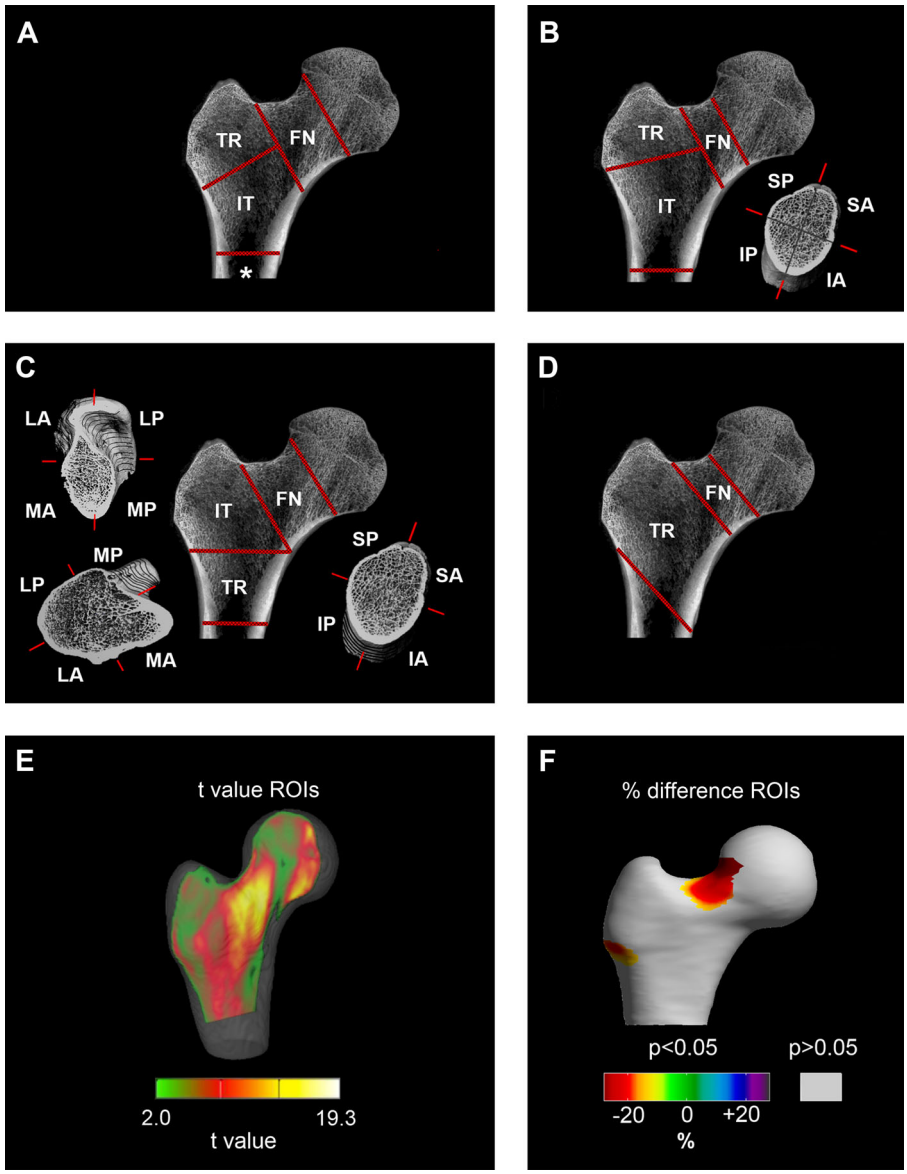

Fig. 1. Summary of the image analysis techniques available to measure cortical bone in vivo. Techniques in (*A–D*) are conventional approaches that are based on predefined regions of interest and estimates are average values over those regions.[10,27–29,31–34] The methods differ both in the definition of ROIs as well as how cortical and trabecular compartments are separated and how structural parameters, such as thickness, area and volume are measured. Techniques in (*E*, *F*) are computational anatomical methods that consider the whole structure to identify ROIs using statistical parametric mapping.[30,35,43–44] These procedures allow researchers to determine if there is a statistically significant mean difference between groups (or with time, with treatment, with placebo, etc.) and to show the site(s) and magnitude of those differences on a femur model. The results from these methods are usually visualized with feature maps. The colorized scale usually represents the values themselves but separate maps of *t* values or *p* values can also be generated. (*A*) ROIs as defined by MIAF-Femur software. Cortical (and subcortical) density, thickness, area and volume are measured in three regions: FN, TR (greater trochanter), and IT (includes a half of the lesser trochanter). (*B*) ROIs as defined by Mindways software. Cortical density, thickness, and area are measured in four regions: FN, TR (greater trochanter), IT (including the lesser trochanter) and total proximal femur that comprising all three regions. An additional module (BIT2) allows further subdivision of the FN region into anatomical quadrants (cross-section inset). (*C*) ROIs as defined by Yang and colleagues. Cortical density and thickness measured in four regions: FN, TR (greater trochanter), TR (including lesser trochanter) and total proximal femur comprising all regions. In addition, each cross-section (FN, IT, and TR) can be further subdivided into anatomical quadrants (cross-section insets). (*D*) ROIs as defined by Lang and colleagues, who measured cortical density, thickness, area and volume in three regions: FN, TR (encompassing the greater and lesser trochanters) and total proximal femur comprising both. (*E*) This map shows a mid-coronal cross section of a *t*-map generated using voxel based morphometry (VBM), where nonsignificant voxels have been rendered transparent and significant voxels assigned a degree of opacity based on their *t* values. The map displays differences in vBMD between younger and older American women (adapted from[35]). (*F*) A color map displaying the average percentage difference in cortical thickness between women with femoral neck fracture and age-matched controls. ROI identification using cortical bone mapping involves registration of 3D cortical bone maps to an average femur surface followed by multivariate modeling using Surfstat software (adapted from[43]). FN = femoral neck; TR = trochanter; IT = intertrochanter; SA = superoanterior; SP = superoposterior; IA = inferoanterior; IP = inferoposterior; MA = medioanterior; LA = lateroanterior; MP = medioposterior.

intertrochanteric, and trochanteric ROIs (Fig. 1*C*). In most quadrants, density and thickness were significantly lower in cases compared to the subcohort. They also merged quadrants into simple lateral and medial halves of the femoral neck (superior and inferior respectively), plus trochanteric (lateral and medial) for discrimination analyses. Lower cortical density and thickness in all regions was significantly associated with hip fracture except cortical density of the inferior neck. Once again, cortical measurements did not predict hip fracture independently of total hip DXA aBMD; interestingly, trabecular density of the femoral neck and medial trochanteric regions did. The regression model combining age, total hip DXA aBMD, and trabecular density best predicted hip fracture (area under the receiver operating characteristic curve [AUC] of 0.901, 95% confidence interval [CI] of 0.852–0.950). It should be noted that there were relatively few hip fractures in comparison with the number of variables and further study of this large and unique cohort is needed. More recently, Yang and colleagues[47] identified deficits in bone density and cortical thickness throughout the proximal femurs of 50 British postmenopausal women compared with controls in a matched case-control study. Cortical thickness and density discriminated fracture cases from controls independently of DXA aBMD, although substantial changes in bone parameters may have occurred in the 3 weeks to 3 months between fracture and CT assessment.

The AGES-Reykjavik study is a single-center prospective population study of Icelandic men and women with baseline CT of 5500 individuals obtained between 2002 and 2006. In a prospective analysis of a subset from this cohort, QCT analysis of the mid-femoral neck (Fig. 1*B*) was performed to measure cortical thickness in different regions and to predict incident femoral neck and trochanteric fracture in a case-control analysis. Fifty-five men were included who subsequently fractured (31 FN, 24 TR) versus 111 age-matched male controls, and 88 women with hip fracture (47 FN, 41 TR) versus 187 female controls.[48] Cortical thickness estimated in the superior region of the femoral neck was a stronger predictor for hip fracture than the inferior region in both sexes. There were significant gender differences in cortical thickness measurements in the control group but not in the case group, implying that the mechanism causing bone thinning in "at risk" individuals might be similar in men and women. Cortical thickness estimated in the superoanterior quadrant (SA; Fig. 1*B*) was the best discriminator of cases from controls. Trochanteric fracture cases were thinner in the inferior neck than femoral neck cases. In multivariate analysis for the risk of femoral neck fracture, SA quadrant cortical thickness was important in both women and men, and remained a significant predictor after adjustment for femoral neck DXA-like aBMD. In those men who sustained trochanteric fracture, both cortical thickness and total hip DXA-like aBMD made independent contributions to fracture prediction. The results from this study suggest that cortical thinning superiorly in the hip might be of importance in determining resistance to femoral neck fracture, as predicted from extensive preclinical studies.[49]

French and English women (age $\geq$60 years) were recruited to a QCT hip fracture case-control study involving 47 women with fracture (24 FN, 23 TR) and 60 controls (Fig. 1*A*).[50] Cortical thickness and trabecular density were again independent predictors of hip fracture risk. Average cortical thickness was significantly lower in the femoral neck, trochanteric, and intertrochanteric ROIs in the hip fracture group. Only in the trochanteric ROI were cortical density and cortical volume significantly lower in fracture cases, whereas trabecular (and integral) density measurements were significantly lower in all ROIs in the hip fracture group. Once more, overall hip fracture discrimination was not improved compared to DXA aBMD. Using logistic procedures to discriminate fractures from QCT measures only, the authors found that a model combining trochanteric trabecular density and mean trochanteric cortical thickness provided the best discrimination of trochanteric fractures from controls, whereas the best discriminator for femoral neck fractures was trabecular bone density in the femoral head. However, the sample size was relatively small for the discrimination of fracture types.[50]

Concerning the mid-femoral neck (Fig. 1*B*, but using the center of mineral mass to divide sectors rather than center of area), two small case-control studies were carried out to investigate determinants of trochanteric ($n = 16$) and femoral neck fracture ($n = 20$) among elderly Japanese women.[26] No differences were found in trabecular density between the controls and fracture cases. Instead, both fracture groups had lower cortical density, bone size, a larger medullary area, and a thinner cortex compared to controls. Thus there may be important differences between populations and fracture types in the structural determinants of hip fracture.

Moving to SPM methodology using VBM, two QCT case-control studies (one of Chinese women, one of Icelandic women) were used to identify the location, magnitude and statistical significance of mean differences between groups with and without fracture.[30,35] SPM was used first on hip CT data by application to the nonfractured hip of 37 fracture cases and 38 age-matched controls in Chinese women, with results showing that density differences were not uniformly distributed.[30] The main differences were actually localized in three new ROIs: medially and superiorly in the femoral head, superiorly in the femoral neck, and inside the trochanter. In a later, larger study, analysis was done in a group of older women from the Icelandic AGES study with ($n = 74$) and without ($n = 148$) incident hip fracture 4 to 7 years after their baseline CT scans.[35] SPM showed that women who fractured their hips had relative deficits in the superior cortex, in trabecular bone regions, as well as in the inferior aspect of the femoral neck and the intertrochanteric region. Even though the mechanical implications of these differences are somewhat conjectural, these foci of bone loss coincide with the locations of highest stresses in a sideways simulated fall configuration and the least loaded locations in a stance configuration.[17] Recently, this study has been reanalyzed to include the effects of shape variation in addition to density distribution in TBM, a modification of VBM.[44]

A further CT study of women from the Czech Republic used CBM to examine cortical thickness over the entire proximal femoral cortex to identify and visualize surface ROIs where cases and controls differed significantly.[43] Seventy-five women with acute hip fracture (36 FN, 39 TR) were compared with 75 age-matched and sex-matched controls, the results showing a marked phenotypic difference between the hips of patients sustaining the two hip fracture types. The femoral neck fracture cases had a thumbnail sized patch of 30% thinner cortex at the superoanterior femoral neck (Fig. 1*F*), which was not apparent in the trochanteric fracture cases, confirming the importance of this zone.[48] Cases who had sustained a trochanteric fracture had a thinner cortex on the trochanter compared to controls. The similarities in location of the ROIs using SPM and traditional femoral neck ROIs are notable,[30,35,43,48] but sensitivity analyses are awaited to establish the ability of VBM and CBM to predict incident fracture.

The studies discussed above have confirmed that QCT-derived measurements of the hip cortex are strongly related to hip fracture risk and can provide useful information concerning causation of hip fracture. Parametric methods have generated new targets for treatment: ROIs that differ between those with fracture and those without. Whereas VBM-derived ROIs appeared to improve specificity for hip fracture discrimination in receiver operating characteristic (ROC) analysis compared to traditional ROIs (at a fixed 95% sensitivity),[30] it is worth noting that any QCT technique has yet to outperform DXA aBMD in hip fracture prediction, and a subsequent article from the same team made no reference to comparative fracture discrimination.[35]

Sex Differences Identified From Hip QCT

There is an exponential increase in hip fractures from age 50 to 100 in both sexes, but the rates observed in elderly women are approximately double those observed in elderly men.[51] One reason for this might be differences between the sexes in femoral bone structure that persist throughout life. Figure 2 describes some of these differences, as well as ageing differences identified in QCT studies.

Riggs and colleagues[52] examined a single cross-section of the mid-femoral neck in a cohort of U.S. men ($n = 323$) and women ($n = 373$) from 20 to 90 years old who had undergone hip QCT. Hip scans were examined by applying in-house scripts.[39] The femoral neck CSA of young men (aged 20–29 years) were one-third larger on average than women of the same age, with higher cortical density. Differences were maintained into old age.[53] Similar sex differences were observed in older Icelandic individuals among a large population-based cohort of 1715 older Icelandic individuals aged 67 to 93 years (807 men, 908 women) examined as in Fig. 1*D*.[53] In the age group of 67 to 69 years, men had persistently larger femoral neck size (eg, 32% larger minimal CSA) and thicker cortices (9% thicker at the FN region and 11% at the TR region) compared to women.[53] It is worth highlighting that whereas FN cortical density was similar in both sexes (and only slightly lower among women in the TR region), women had substantially lower trabecular density throughout the hip ROIs. Figure 2 illustrates that a proximal femur of a typical older female (aged $\geq$65 years) has few remaining trabeculae in the greater trochanter, which can appear to be empty of medullary bone—this is a consistent finding.[52,53] Although Icelandic men had thicker cortices than women overall, one zone where the sexes did not differ in cortical thickness was at the inferoanterior femoral neck (Fig. 1*B*), a region highly loaded during walking throughout life.[48,54] In a related longitudinal study of older Icelandic adults (100 men and 300 women, mean age 74 years) cortical density of the superior FN region was greater in the men but there was no sex difference in the inferior FN region at either baseline or follow-up.[54] This zone was also relatively protected from age-related bone loss in a cross-sectional study of British women aged 20 to 90 years.[31] The assumption that has been made is that loading of the inferior neck by walking helps preserve this zone from age-related bone loss in both sexes.

With advancing age, endocortical and intracortical remodeling increase, to result in cortical bone that becomes thinner and more porous.[31,48,55,56] It has been hypothesized that endosteal bone loss precedes periosteal apposition,[57] which adapts to maintain whole-bone strength.[58] In addition, some studies using DXA indicate that men undergo a pattern of favorable periosteal apposition to a greater extent than women and that this may contribute to their lower fracture rate.[59–62] However, others using QCT have reported that women exhibit similar periosteal apposition to men.[52,53] It is unclear whether periosteal apposition continues into old age. Kaptoge and colleagues[63] found with DXA that the width of the elderly femoral neck in the anteroposterior projection gradually increased over time. However, in the only two genuinely prospective studies using 3D CT, the size of the femoral neck was unchanged over a follow-up period of 2 and 5 years (Fig. 1*B*).[54,64] In a cross-sectional study, Nicks and colleagues[65] reported that total bone volume measured at different locations in the hip increased from a group of younger to older premenopausal women but not from premenopausal to postmenopausal women (Fig. 1*A*). In the MrOS study, the femoral neck size was minimally related to age in men.[66] Age was also associated with increasing femoral neck size in the cross-sectional AGES study by about 2% per decade in both men and women[53] (Fig. 1*D*). In a small subset from the same cohort (48 men and 59 women) the expansion primarily occurred in the superior to inferior directions.[67] The cross-sectional nature of some of these studies might have introduced secular trends. Clearly there is a need for prospective studies over longer time periods in both sexes.

Changes in Proximal Femoral Cortical Bone With Advancing Age

The ability of cortical bone to resist fracture deteriorates with aging in both men and women. Several studies have examined the effect of aging on cortical bone in the hip with a cross-sectional study design, whereas two studies have been prospective.

A cross-sectional population-based QCT study of American men ($n = 323$) and women ($n = 373$) in the age range 20 to 90 years indicated that elderly hips were larger than young hips, with a larger medullary area and lower cortical area.[52] Cortical bone density was 24% lower in elderly women and 13% lower in elderly men than younger subjects in the cohort. Nicks and colleagues[65] investigated the same women in more detail using a different method (Fig. 1*A*), confirming that there was little cortical bone loss in the proximal femur of premenopausal women, but there was significant loss in postmenopausal women. Most striking in these studies were the different trajectories of bone loss, with cortical bone loss beginning in mid-life, whereas trabecular bone loss was lifelong. In a smaller cross-sectional study of 100 British women, femoral neck cortical bone loss did not show the same initiation phase in mid-life; the decline was apparently linear from 20 to 90 years (Fig. 1*B*).[31]

Age-related changes in bone are not just confined to the femoral neck, but nor are they confined to the cortical compartment. In a cross-sectional study of 908 Icelandic women aged 67 to 93 years, cortical density decreased at both the femoral neck and trochanter among women, but the relative decrement in cortical thickness was greater (Fig. 1*D*).[53] Comparing cortical density with thickness, a cross-sectional study of 107 British and French women aged $\geq$60 years (Fig. 1*A*) demonstrated that cortical density declined with aging, but only in the trochanteric region, whereas cortical thickness decreased significantly with age in the neck, trochanteric, and intertrochanteric regions.[50]

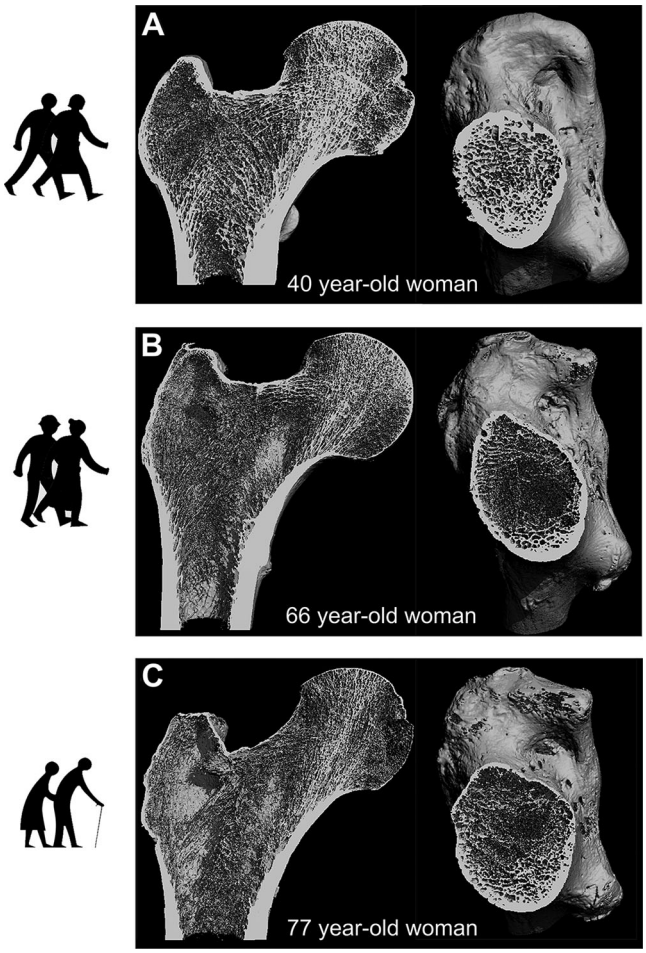

Fig. 2. Some of the major sex and aging differences identified in QCT studies. (*A–C*) Representative female hips from three different age groups. These 3D models of cadaveric hips were made using μCT; mid-coronal cross-section and cross-section through femoral neck of: (*A*) a 40-year-old woman; (*B*) a 66-year-old woman; and (*C*) a 77-year-old woman, respectively. (*A*) Among adults (age range c.20 to 64 years): (1) the superolateral femoral neck cortex is half as thick as the inferomedial cortex in both sexes[31,68]; (2) there is a similar average femoral neck cortical thickness in both sexes[52]; and (3) the male femoral neck remains one-third larger in cross-sectional area than in women throughout life.[52,53] (*B–C*) Among older adults (age range ≥65 years) of both sexes: (1) the superolateral cortex shows three times faster thinning with aging than the inferomedial cortex[54]; (2) women have two times faster cortical thinning with aging than men[54]; (3) the weight-loaded inferomedial cortex is preserved in both sexes[31,35,54]; (4) only one-half of young adult trabecular bone density remains in the very old[31,52]; and (5) very old men have 10% larger femoral neck medullary area and 5% less cortical bone than old men.[66] The femurs were courtesy of the Melbourne Femur Collection, Chairman Professor John Clement (Melbourne Dental School). Traffic sign images are UK crown copyright.

In both sexes, cortical bone distribution is asymmetric in the femoral neck. Returning to the cross-sectional study of 100 British women, even young women had a much thicker inferior than superior cortex. This asymmetry persisted in the old, as illustrated in the femoral neck cross-sections of Fig. 2*A–C*. However, by the ninth decade the femoral neck appears strikingly thinner in the superior cortex, but with relative preservation of the inferior cortex.[31] These results confirm earlier cadaveric studies.[49,68,69] Even among older individuals studied prospectively, superior bone loss continues in both sexes, but at a rate twofold higher in women. Four hundred older Icelandic individuals from the AGES study had CT scans at baseline and 5 years later (100 men and 300 women, aged 66–90 years) (Fig. 1*B*). The principal finding was that, even among older men and women, cortical bone loss in the superior region of the femoral neck was approximately threefold greater than inferior bone loss and the pattern of loss in trabecular bone was similar.[54] Among women, the decline in cortical thickness and density of the superior half of the femoral neck averaged 3.3% per year and 1.2% per year, respectively, contrasting with losses of 0.9% per year and 0.4% per year respectively in the inferior femoral neck. In that study, ROIs were defined by merging superior quadrants (SP and SA) into a "superolateral" half and inferior quadrants (IP and IA) into an "inferomedial" half (Fig. 1*B*). It is noteworthy that a prospective study was needed to demonstrate femoral neck cortical bone loss in men, with several earlier cross-sectional studies of men from the same cohort indicating no age-associated differences in the male FN region cortex.[48,53] The prospective results in Icelandic men are, however, in keeping with a large cross-sectional study of American men ($n = 3358$, aged 65–100 years).[66] Marshall and colleagues[66] found that the oldest men (85+ years) had 5% less cortex and 10% larger medullary volume at the femoral neck compared with the youngest in the study (65–69 years) (Fig. 1*D*).

It is important to note that most of these studies have been conducted in whites, yet substantial ethnic variation in bone structure occurs, with American black and Asian men having thicker cortices with higher trabecular density than American white men.[70] Studies of aging in men and women of different ethnicities are needed, particularly given the rising incidence of hip fracture in Asia. One prospective study of 59 Japanese women (aged 54–84 years) followed for 2 years has been conducted (Fig. 1*B*): cortical thickness in the femoral neck decreased by 1.1% per year, but cortical density was unchanged.[64] One published study and one study in abstract form have examined aging effects using SPM. American women ($n = 349$) were included in a study of age-related bone differences that used intersubject image registration and VBM.[35] Groups were divided into young (age <45 years, $n = 94$), middle-age (≥45 age <60 years, $n = 98$), and older women (age ≥60 years, $n = 157$). The results confirmed the sharp progression of bone loss in the superior cortex of the femoral neck, but also in the trabecular bone of the FN and TR regions (Fig. 1*E*). These results indicated that bone was largely preserved along the trajectories of high load during locomotion (stance) and lost in regions of low load as defined in finite element (FE) studies simulating a stance configuration.[71] Studying 268 British women aged 53 to 93 years, Treece and colleagues[72] found a similar pattern of cortical mass preservation with age using CBM. These tools give researchers the ability to examine drug and exercise effects, with the aim of investigating whether interventions can preserve bone in the unloaded as well as loaded areas.

The Effect of Drug Treatment on Cortical Bone in the Hip

In the previous sections we have highlighted specific defects present in the femurs of older people who go on to fracture their

hips, some of which coincide with age-related changes. Here we review the effects of drugs on these specific QCT measures. Older women with osteoporotic fractures or low DXA aBMD have been enrolled in large randomized controlled trials (RCTs) to demonstrate the efficacy of antiosteoporotic drugs. Although few hip fractures occurred in these trials, older women randomized to receive alendronate, risedronate, zoledronate, and denosumab had approximately one-half as many hip fractures as those receiving placebo.[73] Surprisingly little is known about how these drugs prevent hip fractures. Plotting the events by group for each trial, it is notable that fracture rates diverge then appear to run in parallel; in other words there is a fairly early prevention of fracture, and then a gradual increase in hip fractures in both groups at a similar rate. Could strengthening of specific hip defects be the explanation for the fairly rapid prevention of fractures with these drugs? Or among a population of women already selected for their fragile bones, do the drugs have focal effects on weak areas, preventing fractures that occur spontaneously, or during trips and stumbles?[4,74] The prevention of fractures cannot be fully explained by enhancement in DXA aBMD, so we turn to studies using QCT for possible answers.

The effects of bisphosphonate treatments such as alendronate (ALD), risedronate (RIS), zoledronic acid (ZOL), and ibandronate (IBD) are to decrease osteoclastic resorption, and hence decrease the rate of bone turnover, whereas anabolic treatments such as parathyroid hormone (PTH) and teriparatide (TPTD) stimulate bone remodeling and ultimately bone formation. Increasingly, new drug trials have included smaller substudies involving serial clinical CT in order to investigate the effect of these drugs at the hip.

We have to rely on comparator studies to examine the effects of alendronate. Black and colleagues[75] evaluated the effects of PTH and ALD alone and in combination using hip QCT (Fig. 1*D*) among postmenopausal women with osteoporosis (aged 55–85 years). Women were randomized to daily full-length PTH (1–84, $n = 119$ women), ALD (10 mg/d, $n = 60$), or both ($n = 59$) and were followed for 12 months. Trabecular density increased significantly within all treatment groups but with no significant difference between groups. Total hip cortical density increased by 1.2% with ALD, whereas it decreased by 1.7% with PTH treatment and was unchanged with combination. The study was then extended for a further year, after which cortical density had decreased by 2% to 3% from baseline with ALD; the same was seen with PTH and placebo, and PTH given for 2 years.[76] Conversely, with combination PTH plus ALD for 1 year followed by ALD in the second year, cortical density was maintained. Given the expected mechanism of action of ALD, a surprising finding was that cortical volume appeared to increase slightly during ALD therapy, although less than was seen with PTH alone. This might signify that with ALD treatment, a greater proportion of endocortical "trabecular" voxels became classified as "cortical" voxels when using an analysis technique based on thresholding. A randomized double-blind study conducted by McClung and colleagues[77] compared the effect of ALD (10 mg/d, $n = 30$) versus TPTD (20 μg/d, $n = 26$) in postmenopausal women with osteoporosis. Cortical density in the FN region (Fig. 1*B*) was significantly different between ALD and TPTD groups, increased by 7.7% in ALD group, and decreased by 1.2% in TPTD group.

The effect of once-yearly zoledronic acid (5 mg intravenously [iv] per annum) on hip QCT parameters (Fig. 1*A*) was examined by Eastell and colleagues[78] in a subset of postmenopausal women (ZOL, $n = 93$; placebo, $n = 86$) from the large HORIZON-PFT RCT. Over 3 years of treatment, ZOL increased total and trabecular hip density versus placebo. Cortical density did not differ significantly between groups but cortical bone volume in the total hip and TR ROIs increased (7% and 9%, respectively) in the treatment group versus placebo, a similar finding to that reported by Black and colleagues[75] studying the effects of ALD. Yang and colleagues[79] used the same HORIZON-PFT substudy data to further divide up the various traditional ROIs into more than 24 individual hip QCT parameters (using a slightly modified version of Fig. 1*C*, with different ROI boundary definitions and names). Statistical correction for multiple comparisons was not described in the paper, but percentage improvements in overall femoral neck density were mostly seen in the superior quadrants. Interestingly, percentage improvements were greater in trabecular than cortical bone of the same region. In fact, the most consistent QCT response variable across the range of antiresorptive trials has been trabecular density.

Although ibandronate has not been proven to prevent hip fractures, its effects on hip QCT parameters were studied during 1 year of therapy in a double-blind RCT versus placebo (women aged 55–80 years, IBD 150 mg by mouth [po] once monthly $n = 39$, placebo $n = 32$).[80] The traditional cortical bone ROIs (Fig. 1*A*) did not show significant changes in any region. However, in a post hoc analysis using the same data which now combined the subcortical and cortical ROIs, IBD increased the density by 1.5% in the total hip "extended ROI" and 2.4% in the trochanteric "extended ROI" versus placebo.[81] Once again, monthly oral IDB for 12 months improved trabecular density in all the extended ROIs versus placebo.

One drug licensed for treating osteoporosis in Japan is an analogue of active vitamin D, eldecalcitol (ELD). Although the drug has not been shown to reduce hip fractures, osteoporotic women receiving ELD have been subject to serial hip QCT analysis in comparison with another licensed active vitamin D analogue alfaclacidol (ALF) (Fig. 1*B*).[82] Here the principal finding was that ELD maintained cortical thickness and "total hip" density, despite a decrease in trabecular density of about 4%. By contrast, ALF treated women lost cortical thickness and "total hip" density, as well as an approximate 7.5% decrease in trabecular density. Cortical mass and density did increase with both treatments.

Neither TPTD nor PTH (1–84) have been shown to prevent hip fracture in RCTs, although Black and colleagues[75,76] did show that hip cortical density decreased over 1 and 2 years of PTH treatment. Although cortical bone volume increased by 4.4% when 1 year of PTH was followed by ALD, it did not when the PTH year was followed by placebo. McClung and colleagues[77] also discovered that cortical density decreased by 1.2% from baseline to 18 months with TPTD, although there was a greater increase in trabecular density with TPTD than with ALD. Keaveny and colleagues[83] found similar results, including a 6.2% reduction in cortical mass with PTH among the same trial participants as in Black and colleagues.[75,76] Borggrefe and colleagues[84] used serial hip QCT scans to perform a segmental femoral neck analysis (Fig. 1*B*) of 52 postmenopausal women (aged ≥55 years) with severe osteoporosis treated with TPTD (20 μg/d). Cortical density declined by 2% after 2 years treatment whereas cortical mineral content and cortical cross sectional area increased by 2.3% and 4.3%, respectively. Total area was unchanged during follow-up. These studies suggest that PTH treatment stimulates endocortical and cortical bone growth, but decreasing cortical density indicates that the new cortical bone is

less packed with mineral (ie, new bone) and/or more porous. Follow on therapy with antiresorptives seems necessary for optimal effects.

Analysis of the same trial participants as in Borggrefe and colleagues[84] given TPTD for 2 years revealed that cortical thickness increased by up to 12% over large areas of the hip,[33] including several sites of focally low bone thickness and mass that were previously identified in women with hip fracture.[33,43] However, cortical mass only increased significantly in a very small intertrochanteric area.[33] These results contrast with the striking effects of the antiresorptive denosumab on cortical mass, shown using a range of techniques (Fig. 1*A*, *B*; CBM).[85–87] In a subset of postmenopausal women from the FREEDOM trial who received 60 mg of denosumab versus placebo every 6 months for 3 years, denosumab-treated women showed a progressive increase in cortical mass and thickness over time.[88] As was seen with bisphosphonates, the relative improvements were greatest in the trabecular compartment.[85,87] Cortical mass increased almost throughout the hip, being associated with smaller magnitude cortical thickening (which is believed to represent the infilling of cortical and endocortical pores in the early phase of treatment).[85,88] Odanacatib is an inhibitor of cathepsin K and has been investigated in two recent studies.[89,90] After 2 years, Brixen and colleagues[89] found that trabecular (but not cortical density) differed significantly between odanacatib and placebo in the hip. Cortical thickness of the mid-femoral neck increased with treatment but decreased with placebo. In a smaller study by Engelke and colleagues,[90] odanacatib effects were compared with placebo or ALD treatment. In contrast to the results of Brixen and colleagues,[89] odanacatib increased both trabecular and cortical density at the hip but had no effect on cortical thickness. The changes in cortical and trabecular density were similar in the ALD and odanacatib groups.

It remains to be seen which of cortical mass, cortical volume, cortical thickness, or trabecular parameters are more important in preventing hip fracture. The best evidence to date comes from the large trials of antiresorptives, which mostly enhance bone mass, because no hip fracture end-point trials have been conducted with TPTD or PTH. However, absence of evidence should not preclude further efforts toward preventing hip fracture with anabolic compounds. The results from QCT hip studies, particularly those including sequential antiresorptives after anabolic drugs, are very encouraging.

Limitations

There have been numerous technical approaches to try and overcome the inherent inaccuracies involved in measuring thin cortical bone using clinical QCT. The spatial resolution of the CT scanners is limited such that measurements may be under- or overestimated because of trabecular bone adjacent to the endosteal surface or soft tissue adjacent to the periosteal surface. Both in-plane resolution and slice thickness cause partial volume artifacts that affect cortical measurements.[38,91–93] Because the femoral neck is oriented obliquely to the scan plane it is affected more than other regions, although one of the techniques takes this into account.[32,33] A cortical thickness of 2 to 2.5 mm is generally required for accurate cortical density evaluation in clinical CT,[91] whereas cortical density values below this threshold are typically a function of the cortical thickness and cortical porosity because of partial volume averaging. This means that a thin structure will appear to have lower density and less accurate thickness. The partial volume effect tends to make trabecular bone close to the endosteal boundary appear more dense and cortical bone less dense than they really are.[38,94] Despite these limitations, cortical bone measurements are associated with hip fracture in many studies, and whereas cortical density and thickness measurements are challenging, changes in these variables can be detected more accurately when the difference exceeds a certain threshold.[93] Although the techniques that we have reviewed differ in how cortical bone and trabecular bone are delineated (as well as in the location and method of measurements), no studies directly comparing the methodologies have been reported. Despite this, the major conclusions from the clinical studies are remarkably consistent, whichever methods have been applied.

Conclusion

Clinical QCT studies of the hips have led to a greater understanding of the patterns of bone loss associated with hip fracture, age-related changes, and the effects of drugs used to treat osteoporosis. From these studies, particular regions of the proximal femoral cortex have been identified, not only as sites relevant to fracture causation, but also as sites which are novel targets for therapeutic and other interventions. Results from QCT studies of "traditional" ROIs and those derived from parametric methods (SPM and VBM) seem to agree, largely on where the critical changes associated with ageing and hip fracture occur. However, it is not yet known whether these CT-derived bone measurements will improve fracture prediction compared with existing clinical techniques, and further prospective studies are awaited. It is also worth remembering that cortical bone, although of crucial importance in determining hip fracture and treatment response, is one of many variables which need to be considered in efforts to understand and prevent the burden of age-related hip fractures. The advances in clinical CT imaging and image processing that we have reviewed here continue to play a key role in meeting this challenge.

Disclosures

KESP is co-inventor of a related patent. Image data processing systems. GB0917524.1 and US-2012-0224758-A1. This does not alter the authors' adherence to all the JBMR policies on sharing data and materials. KESP: payment for lectures to institution (Amgen Inc.), research grants to institution (Amgen Inc. and Lilly), advisory board fees to institution (Amgen Inc.). TDT: payment for a lecture (Amgen Inc.). FJ states that she has no conflicts of interest.

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