The Distribution and Importance of Cortical Thickness in Femoral Neck and Femoral Shaft and Hip Fracture and Lower Limb Fracture

Fjóla Jóhannesdóttir

Faculty of Industrial Eng., Mechanical Eng.
And Computer Science
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120 ECTS dissertation submitted in partial fulfillment of a
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Advisor
Gunnar Sigurðsson, MD PhD FRCPE

PhD Committee
Gunnar Sigurðsson, MD PhD FRCPE
Thor Aspelund, PhD
Sigurður Brynjólfsson, PhD
Vilmundur G. Guðnason, MD PhD

Opponents
Mary L. Bouxsein, PhD
Þorvaldur Ingvarsson, MD PhD

Faculty of Industrial Eng., Mechanical Eng. and Computer Science
School of Engineering and Natural Sciences
University of Iceland
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Faculty of Industrial Eng., Mechanical Eng. and Computer Science
School of Engineering and Natural Sciences
University of Iceland
Hjarðarhaga 2-6
107, Reykjavik
Iceland

Telephone: 525 4700

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Abstract

The risk of hip fracture rises rapidly with age, and is notably higher in women. After falls and prior fragility fractures, the main clinically recognised risk factor for hip fracture is reduced bone density. It has been suggested that when falling sideways the crack that initiates an intracapsular fracture often initiates in the supero-lateral cortex. The principal aim of these three study series were to get a better insight into the pathomechanism of hip fracture and possibly improve the assessment of risk of hip fracture. The participants in these study series were all older individuals from the AGES-Reykjavik population based study. In study I (a prospective nested case-control study, cases n=143 and controls n=298); a segmental QCT analysis of the mid-femoral neck was applied to explore the utility of cortical thickness in anatomical quadrants for predicting incident femoral neck and trochanteric fracture. The results elucidated the importance of cortical thickness in the superior surface of the femoral neck with regard to risk of femoral neck fractures in elderly men and women. In study II (a cross-sectional study, n=3,762 and of those 179 fracture cases, thereof 131 hip fractures); using data from a single CT section through the mid-thigh the relationship between muscular and bone variables and their association with incident low-trauma lower limb fractures were studied. The results support the findings from study I that endocortical resorption may be a key process for the development of bone fragility in lower limbs in old age. In study III (a longitudinal study, 100 men and 300 women, median follow-up time 5.1 yr); a segmental QCT analysis was used to assess regional cortical thickness, as well as cortical and trabecular bone mineral density in two anatomic sub-regions, the supero-lateral (superior) and infero-medial (inferior) at the mid-femoral neck. The relative age-related changes were about threefold greater in the superior region than in the inferior region of the mid-femoral neck. Older women lost cortical thickness and cortical BMD more rapidly than men, especially in the superior femoral neck and this is only weakly reflected in the DXA-like results. Since fractures may initiate superiorly, the increased rate of superior femoral neck bone loss in women may contribute materially to the greater risk of femoral neck fracture in elderly women than men. The results support the notion that endocortical resorption and possibly enlargement of intracortical cavities leading to trabecularization of the cortex may be key processes leading to increased bone fragility in the elderly femoral neck. Better understanding of the so far undetermined mechanisms regulating localized bone loss in the elderly proximal femur is an important topic for future research because of the marked difference in regional bone loss between individuals and also between the two sexes.

Keywords: Cortical thickness; Hip fracture; Quantitative computed tomography; Proximal femur; BMD; Mid-thigh; Muscle-bone relationship; Aging

Útdráttur

Áhætta á að mjaðmarbrotna eykst hratt með aldri og er talsvert hærri meðal kvenna. Beinþéttni í nærenda lærleggs er sá þáttur sem mest hefur verið notaður sem forspárþáttur um mjaðmarbrot. Rannsóknir hafa bent til að við fall á stærri lærhnútu myndast oftast sprunga, sem endar með broti innan liðpokans, á efra yfirborði miðs lærleggsháls. Meginmarkmið þessara þriggja rannsókna var að öðlast meiri skilning á eðli mjaðmarbrota og hugsanlega bæta mat á áhættu á mjaðmarbroti. Allir þátttakendur voru eldra fólk sem var hluti af Öldrunarrannsókn Hjartaverndar. Í rannsókn I (framsýn tilfellaviðmiðuð rannsókn, 143 mjaðmarbrot og 298 einstaklingar í viðmiðunarhópi); var þykkt skelbeins í þversniði á miðjum lærleggshálsi metin út frá sneiðmyndum af mjöðm í líffærafræðilegum fjórðungum sem áhættuþáttur fyrir mjaðmarbroti. Niðurstöðurnar benda til að þunnt skelbein á efra yfirborði miðs lærleggsháls gæti verið ákvarðandi þáttur í minnkandi mótstöðu gegn lærleggshálsbroti í eldri einstaklingum. Rannsókn II (þversniðsrannsókn, n=3,762 og af þeim brotnuðu 179, þar af mjaðmarbrot 131) byggir einnig á CT-mælingum á skelbeinsþykkt en í miðjum lærlegg þar sem samband milli vöðva- og beinabreyta og tengsl þeirra við áverka lítil neðri útlimabrot voru rannsökuð. Þessi rannsókn benti einnig í sömu veru um mikilvægi þykktar skelbeins eða öllu fremur þynningar á skelbeini vegna beinniðurbrots innan frá mergholi sem er hugsanlega lykilatriði í þróun á brothættu í neðri útlimum hjá eldra fólki. Í rannsókn III (langsniðsrannsókn, 100 karlar og 300 konur, miðgildi eftirfylgni tíma 5.1 ár), var skelbeinsþykkt í þversniði á miðjum lærleggshálsi metin ásamt beinþéttni skelbeins og frauðbeins út frá sneiðmyndum í tveimur líffærafræðilegum svæðum, efri hluta (supero-lateral) og neðri hluta (infero-medial) miðs lærleggsháls. Hlutfallslegar aldursbreytingar voru þrefalt meiri í efri hluta en neðri hluta á miðjum lærleggshálsi. Eldri konur töpuðu skelbeinsþykkt og skelbeinsbeinþéttni mun hraðar en karlar, sérstaklega í efri hluta lærleggsháls og það endurspeglast ekki nema að litlu leyti í niðurstöðum sem jafngilda DXA. Þar sem brot byrja mögulega í efri hluta lærleggsháls er það hugsanlega aukið beintap í efri hluta lærleggsháls sem veldur því að eldri konur eru í meiri áhættu á að brotna á lærleggshálsi en karlar. Niðurstöðurnar styðja þá tilgátu að beinniðurbrot innan frá mergholi og stækkun á holrúmum innan í skelbeini, sem leiðir til að skelbeinið verður frauðkennt, séu lykilferlar sem leiða til aukinnar brothættu á lærleggshálsi meðal eldra fólks. Meiri skilningur á þeim óþekktu þáttum sem stýra staðbundnu beintapi í lærleggshálsi eldra fólks er mikilvægt rannsóknarefni sérstaklega vegna merkjanlegs muns í svæðisbundnu beintapi milli einstaklinga sem og milli kynja.

Lykilorð: Skelbeinsþykkt; Mjaðmarbrot; Magnbundin sneiðmyndataka; Nærendi lærleggs; Beinþéttni; Mitt læri; Tengsl vöðva og beins; Öldrun

List of publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals (I-III):

I. **Distribution of Cortical Bone in the Femoral Neck and Hip Fracture: A Prospective Case-Control Analysis of 143 Incident Hip Fractures; the AGES-REYKJAVIK Study.**
Fjola Johannesdottir, Kenneth E. Poole, Jonathan Reeve, Kristin Siggeirsdottir, Thor Aspelund, Brynjolfur Mogensen, Brynjolfur Y. Jonsson, Sigurdur Sigurdsson, Tamara B. Harris, Vilmundur G. Gudnason and Gunnar Sigurdsson
Bone 48, 1268-1276 (2011)

II. **Mid-Thigh Cortical Bone Structural Parameters, Muscle Mass and Strength, and Association with Lower Limb Fractures in Older Men and Women (AGES-Reykjavik Study)**
Fjola Johannesdottir, Thor Aspelund, Kristin Siggeirsdottir, Brynjolfur Y. Jonsson, Brynjolfur Mogensen, Sigurdur Sigurdsson, Tamara B. Harris, Vilmundur G. Gudnason, Thomas Lang and Gunnar Sigurdsson
Calcified Tissue International 90, 354- 364 (2012)

III. **Similarities and Differences between Sexes in Regional Loss of Cortical and Trabecular Bone in the Mid-Femoral Neck: The AGES-Reykjavik Longitudinal Study**
Fjola Johannesdottir, Thor Aspelund, Jonathan Reeve, Kenneth E. Poole, Sigurdur Sigurdsson, Tamara B. Harris, Vilmundur G. Gudnason and Gunnar Sigurdsson
Manuscript submitted to Journal of Bone Mineral Research.

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Conference publications that are not included in this dissertation:

A. **Femoral Neck Cortical Thickness Declines in the Elderly Three-fold Faster Superiorly than Inferiorly: The AGES-REYKJAVIK Longitudinal Study.**
Fjola Johannesdottir, Thor Aspelund, Jonathan Reeve, Kenneth E. Poole, Sigurdur Sigurdsson, Tamara B. Harris, Vilmundur G. Gudnason, Gunnar Sigurdsson
34th Annual Meeting, The American Society of Bone and Mineral Research, Minneapolis. 12-15 October 2012

B. **Testing the mechanostat theory: the relationship between CT bone and muscle variables in mid-thigh in elderly men and women and association with incident lower limb fractures**
Fjola Johannesdottir, Thor Aspelund, Kristin Siggeirsdottir, Byrnjolfur Y. Jonsson, Brynjolfur Mogensen, Sigurdur Sigurdsson, Tamara B. Harris, Vilmundur G. Gudnason, Thomas F. Lang, Gunnar Sigurdsson.
Front. Endocrin. 2011 joint meeting of the Bone Research Society & the British Orthopaedic Research Society. 27-29 June 2011

C. **Þunnt skelbein aðgreinir einstaklinga með mjaðmarbrot frá óbrotnum hjá báðum kynjum: Öldrunarrannsókn Hjartaverndar**
Fjola Johannesdottir**,** Kenneth E. Poole, Jonathan Reeve, Kristin Siggeirsdottir, Thor Aspelund, Brynjolfur Mogensen, Brynjolfur Y. Jonsson, Sigurdur Sigurðsson, Tamara B. Harris, Vilmundur G. Guðnason, Gunnar Sigurðsson
The Icelandic Medical Journal 66 Suppl, 19, (2011)

D. **A Similar Cortical Thickness Threshold discriminates Femoral Neck Fracture Cases from Controls in both Sexes – AGES-REYKJAVIK Study**
Fjola Johannesdottir, Kenneth E. Poole, Jonathan Reeve, Kristin Siggeirsdottir, Thor Aspelund, Brynjolfur Mogensen, Sigurdur Sigurdsson, Tamara B. Harris, Vilmundur G. Gudnason, Gunnar Sigurdsson
Bone 47 Suppl, S89, (2010)

E. **The Distribution of Cortical Bone in the Femoral Neck and Hip Fracture: A Prospective Case-Control Analysis of 143 Incident Hip Fractures from the AGES-REYKJAVIK Study**
Fjola Johannesdottir**,** Kenneth E. Poole, Sigurdur Sigurdsson, Brynjolfur Mogensen, Kristin Siggeirsdotti, Byrnjolur Y. Jonsson, Tamara B. Harris, Vilmundur G. Gudnason, Gunnar Sigurdsson
J Bone Miner Res 24 Suppl, S249, (2009)

Declaration of contribution

Paper I – Fjola Johannesdottir analyzed the QCT data and assessed the cortical thickness measurements as well as other bone measurements. She did test the reproducibility of the method in vivo and pre-processed the data for the paper. She did the statistical analyses and interpreted the results. She wrote the manuscript and corresponded with the journal.

Paper II - Fjola Johannesdottir did the statistical analyses and interpreted the results. She wrote the manuscript and corresponded with the journal.

Paper III - Fjola Johannesdottir analyzed the QCT data and assessed the cortical thickness and bone mineral density measurements. She tested the reproducibility of the method, standardized the method for longitudinal reading and pre-processed the data for the paper. She did the statistical analyses and interpreted the results. She wrote the manuscript and will correspond with the journal.

Table of Contents

List of Figures

List of Tables

Abbreviations

AGES-Reykjavik study	Age Gene/Environment Susceptibility-Reykjavik Study
ANOVA	one-way analysis of variance
BMC	bone mineral content
aBMD	areal bone mineral density
vBMD	volumetric bone mineral density
BMI	body mass index
BR	buckling ratio
CI	confidence interval
CortvBMD	cortical volumetric bone mineral density
CV	coefficient of variation
DXA	dual energy X-ray absorptiometry
ER-α	estrogen receptor
Est CTh	estimated cortical thickness
FE	finite element
FN	femoral neck
FN aBMD	DXA-equivalent for the total femoral neck aBMD
FN IntvBMD	mean integral vBMD measured from mid-femoral neck
HR	hazard ratio
I	inferior
iCThi	cortical thickness index
IntvBMD	integral volumetric bone mineral density
IA	inferio-anterior
IP	inferio-posterior
MA	medullary area
QCT	quantitative computed tomography
S	superior
SA	supero-anterior
SD	standard deviation
SP	supero-posterior
shaft CSA	total cross-sectional periosteal area of femoral shaft
TR	trochanter
TrabvBMD	trabecular volumetric bone mineral density

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1 Introduction

1.1 Motivation and background

Osteoporosis is one of the major public health problems facing the elderly population. Lifetime risk of any osteoporotic fracture is very high and lies within the range of 40-50% in women and 13-22% for men (Johnell and Kanis 2005). Hip fracture is increasing worldwide due to rapidly aging populations (Kanis 1993) and is a serious injury that can lead to permanent disability or mortality (Moyad 2003). Hip fracture alone affects over 300.000 elderly in the US annually and it results in an annual cost over 10 billion dollars (Burroughs and Walker 2012). In Iceland we can expect 250-300 hip fractures yearly (currently being addressed by GS). Ambulation after a hip fracture is almost impossible until the fracture has been treated surgically, and 1 out of every 4 to 5 patients does not survive more than 1 year after the fracture (Moyad 2003; Johnell and Kanis 2005). In 90% of all hip fracture cases, a fracture is sustained through a fall (Schwartz et al. 1999).

Current methods of evaluating the risk of a proximal femur fracture are based on the idea that reduced bone strength is related to fracture incidence and bone mineral density (BMD) (Riggs et al. 1982; Lang et al. 1991; Jergas et al. 1992). Dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) are the most popular and effective methods to obtain estimates of BMD. Attempts to improve these techniques have been including simple measures of femoral geometry in the evaluation (Lang et al. 1997; Mayhew et al. 2005; Sigurdsson et al. 2006; Cheng et al. 2007), or by performing 2-D structural engineering analyzes (Charles et al. 2001; Kaptoge et al. 2003; Lloyd et al. 2004; Petit et al. 2005) and recently whole bone strength of proximal femur has been estimated in vivo using finite element analysis in population based studies (Orwoll et al. 2009; Keaveny et al. 2010; Keyak et al. 2011; Shreyasee et al. 2011; Lang et al. 2012; Srinivasan et al. 2012). Neither decreasing BMD nor an increased risk of falls appears to fully explain the increase of hip fracture with age and yet BMD alone measured by DXA or QCT in femoral neck does not satisfactorily identify individual subjects at high risk of fracture (Black et al. 2008).

In normal gait, the greatest stresses occur in the sub-capital and mid-femoral neck region (Lotz et al. 1995). Within these regions, maximum compressive stresses occur inferiorly and smaller magnitude of tensile stresses occur superiorly (Lotz et al. 1995). During a sideways fall on the greater trochanter, the stress state is reversed. The greater compressive stresses and strains occur in the superior femoral neck while the lower tensile ones occur in the inferior region (Lotz et al. 1995; Verhulp et al. 2008). Bones generally expand with age by periosteal apposition (Riggs et al. 2004). It appears to be a homeostatic adaptation to bone loss that preserves bending resistance. If age-related endocortical bone resorption producing a thin cortex -- it is theorized that we could have a situation in which the cortex has now become so progressively thinned that a person can have local instability with a precipitous loss of strength and structural failure.

1.2 The aim of the project

A novel clinical evaluation of hip structure should preferably achieve a better prediction of hip fractures and also guide an appropriate intervention (Bouxsein and Delmas 2008). The principal aim of our study was to gather more knowledge about hip fracture pathomechanism and possibly improve the assessment of risk of hip fracture. A prospective nested case-control study was carried out to analyze the circumferential differences in cortical thickness of the mid-femoral neck as a risk factor for low trauma hip fractures (n=143) in older women and men. This case-control study was followed by a longitudinal study (n=300 women, n=100 men) where changes in regional cortical thickness, cortical BMD and trabecular BMD as well as integral (i.e., cortical plus trabecular) BMD at mid-femoral neck were assessed with advancing age. In addition to the investigation of the importance of cortical bone in the mid-femoral neck, a cross-sectional study was done to study the cortical thickness and size of medullary area in the mid-femur in older people (n=1838 men and n=1924 women) and the association of muscle and bone parameters in the mid-thigh with incident low-trauma lower limb fracture.

1.3 Overview of the dissertation

This dissertation is organized in the following manner:

Bone biology is examined in chapter 2. Bone structure and bone cells are described. Bone modelling and remodelling is discussed together with osteoporosis. In chapter 3 the factors that contribute to bone strength as well as the mechanical properties of both cortical and trabecular bone tissues are reviewed as well as the age-related changes in bone strength are discussed. The biomechanics of a proximal femur fracture is reported in chapter 4. In chapter 5 the main objectives of this project are summarized and the applied methodologies in chapter 6. Summary of key results is given in chapter 7. In chapter 8 the results are discussed along with the limitations of the study and future works.

2 Bone biology

2.1 Introduction

The skeletal system is made up of bones and connective tissue that joins them. Bone is the main part of the system and the function of bone requires it to be stiff and strong. The purposes of bones are; to provide supporting structure throughout the vertebrates, to be the levers of the locomotion system to which muscle and ligaments are attached and to act as a metabolic reservoir of minerals (e.g. calcium), in addition to produce blood cells and protect internal organs (Stevens and Lowe 1997; Jee 2001). Bone is a remarkable material having unique material properties and the ability to repair itself and adapt by biological remodelling and turnover, by altering its mass, shape, and properties, to meet the mechanical demands placed on it (Frost 1987; Rittweger 2008). Bone require mechanical stress in order to grow and strengthen therefore physical activity is important to develop and maintain bone strength.

2.2 The structure of bone

The composition of bone is more complex than most engineering composites as there is no level of organization at which one can truly be said to be looking at bone as such. This discussion starts at the lowest level and works up to a brief description of the variety of structures seen in whole bones.

2.2.1 Composition of bone

Bone is composed of 65% (by weight) mineral (inorganic phase) and 35 % organic matrix (consist of 90% collagen and 10% of various noncollagenous proteins), cells and water (Jee 2001). At the lowest level, bone can be considered to be a composite material consisting of collagen that is impregnated and surrounded by bone mineral. The bone mineral is in the form of small crystal in the shape of needles, plate, and rods located within and between collagen fibers. The mineral is largely an impure form of naturally occurring calcium phosphate, most often referred to as hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$. Calcium compounds provide stiffness and strength but collagens provide ductility and toughness (Currey 2003). The water content is important to bone strength and plays a role in the viscoelastic behaviour of bone, e.g. in withstanding compressive forces and maintaining bone health. During growth, the amount of organic matrix per unit volume remains relatively constant, while the amount of water decreases and the proportion of bone mineral increases. The reduction of water content results in a stiffer bone in adults than in children. The mineralized collagen fibril is arranged in a number of ways to produce the overall composite.

2.2.2 Bone cells

The major cellular elements of bone include osteoclasts, osteoblasts, osteocytes and bone-lining cells. They are briefly described here (Stevens and Lowe 1997; Noble and Reeve 2000; Jee 2001; Currey 2002).

Osteoblasts are bone forming cells and located on the surface of bone (periosteum and endosteum). They initially lay down the collagenous matrix, osteoid, participate in the mineralization and regulate the flux of calcium and phosphate in and out of bone. The active osteoblasts possess receptors to many bone agents, such as parathyroid hormone (PTH), parathyroid hormone-related protein (PTHrP), prostaglandins, vitamin D metabolites, gonadal and adrenal steroids and certain cytokines, lymphokines etc. .

Bone-lining cells cover most resting surfaces of bones and control the movement of ions between the body and the bone. The cells are believed to be derived from inactive osteoblasts and/or osteblast precursors that have differentiated and flattened out on bone surfaces. Bone-lining cells can form bone in response to bone anabolic agents and may be involved in homeostatic, morphogenetic and restructuring processes that constitute regulation of bone mineral mass and architecture.

Osteocytes are the principal cell type in mature bone and derived from osteoblasts. They are embedded into bone matrix, residing in lacunae and communicate with neighbouring osteocytes and with osteoblasts and bone lining cells by means of processes that are housed in little channels (canaliculi). The osteocytes play a key role in homeostatic, morphogenetic, and restructuring processes of bone mass that constitute regulation of mineral and architecture. Osteocytes respond to mechanical load and changes in bone metabolism. They transmit the mechanical load through intracellular and extracellular signal transmitters to induce bone formation or resorption or combination of both. The osteocytes may (Jee 2001) (1) stabilize bone mineral by maintaining an appropriate local ionic milieu, in collaboration with the bone-lining cells that controls the efflux of calcium ions, (2) detect microdamage, and (3) respond to the amount and distribution of strain within bone tissue that influence adaptive modelling and remodelling behaviour through cell-cell interaction. Aging, loss of estrogen, loading, and chronic glucocorticoid administration is known to increase osteocyte death (Noble and Reeve 2000).

Osteoclasts are bone-resorbing cells, are large, multinucleated cells derived from precursor cells circulating in the blood. Actively resorbing osteoclasts are usually found in cavities on bone surfaces, called resorption cavities. When osteoclasts have done their job they disappear and presumably die. The osteoclasts possesses receptors for calcitonin and responds to parathyroid hormones, $1,25(OH)_2$, vitamin D_3 and calcitonin. Bisphosphonates, calcitonin and estrogen are commonly used to inhibit resorption and are believed to act by inhibiting the formation and activity of osteoclasts and promoting osteoclast death.

2.2.3 Hierarchical levels

Bone tissue is a hierarchical composite at many levels (Rho et al. 1998; Currey 2002) (see; Figure 2.1). At the lowest level (sub-nanostructure), it is a molecular structure of constituent elements, such as mineral, collagen and non-collagenous organic proteins. At

the next level (nanostructure), it is a composite of mineralized collagen fibrils. At the third level (sub-microstructure), these fibrils are arranged in two forms, woven bone and lamellar bone. Woven bone is characterized by irregular organization of collagen fibers and is mechanically weak. Woven bone is usually laid down very quickly and found in situations of rapid growth in children and during initial stages of bone fracture healing. Lamellar bone is more precisely arranged. The collagen fibrils and their associated mineral are stacked in thin sheets called lamellae (3-7μm wide) that contain unidirectional fibrils in alternate angles between layers. Lamellar bone is most common and can take various forms at next level (microstructure). Primary lamellar bone is new bone that consists of large concentric rings of lamellae. The most common type of cortical bone in adult human is called osteonal or Haversian bone, which contains blood vessel capillaries, nerves and a variety of bone cells. The substructure of concentric lamellae, including the Haversian canal, is termed an osteon, looks like a cylinder about 200–250 μm in diameter and lengths of 1-3 mm running roughly parallel to the long axis of the bone. Other channels, called Volkmanns's canals, about the same diameter as Haversian canals, run perpendicular to the Haversian canals, providing radial paths for blood vessels. At the highest hierarchical level (macrostructure), there are two types of bone (1) cortical bone, is made of Haversian systems/osteons and (2) trabecular bone, which is a highly porous cellular solid and the lamellae are arranged in an interconnecting framework of trabeculae in a form a series of rods and plates (a trabecular rod is about 50-300 μm in diameter). This hiearchically organized structure has an irregular arrangement and orientation of the components, making the material of bone heterogeneous and anisotropic.

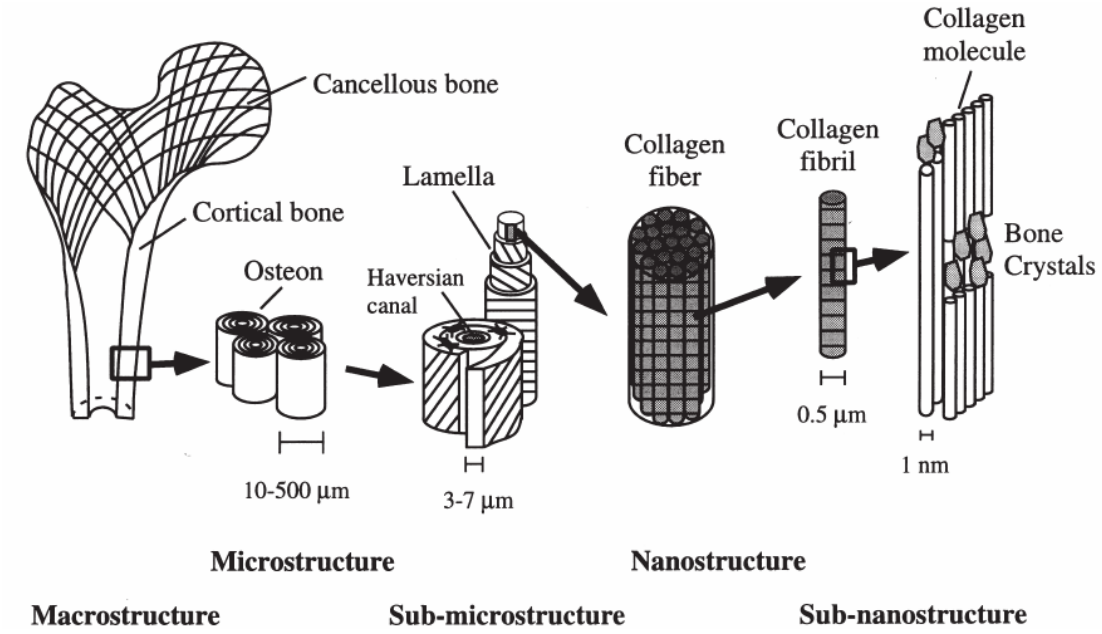

Figure 2.1: Hierarchical structural organization of bone (a) Cortical and trabecular bone (macrostructure); (b) Osteons with Haversian systems (microstructure); (c) lamellae (sub-microstructure); (d) collagen fiber assemblies of collagen fibrils (nanostructure); (e) bone mineral crystals, collagen molecules, and non-collagenous proteins (sub-nanostructure). (Rho et al. 1998) (With permission from Elsevier)

2.2.4 Cortical and trabecular bone

Bone in human and other mammal bodies are composed of two basic structures, trabecular or cancellous bone and cortical or compact bone (Rho et al. 1998; Jee 2001; Currey 2002; Bartel et al. 2006). Trabecular bone is much more porous with 50-90% porosity and is usually found at the ends of long bones, in cuboidal bones and flat bones like the pelvis.The matrix forms an open network of trabeculae (interconnecting rods or plates of bone) and spaces are filled with marrow. The trabeculae are oriented along stress lines and the surface covered with endosteum. Trabeculae have no blood vessels and the canaliculi are opening on surface and nutrition are transmitted through them. Cortical bone is solid, with only spaces in it being for osteocytes, canaliculi, blood vessels and erosion cavities. It is much more dense and stronger than trabecular bone with 5-10% porosity. Approximately 80% of the skeletal mass in the adult human skeleton is cortical bone. It is primarily found in the shaft of long bones and forms the out shell around trabecular bone at the end of joints and the vertebrae. There is a bone section in figure 2.2 showing cortical and trabecular bone.

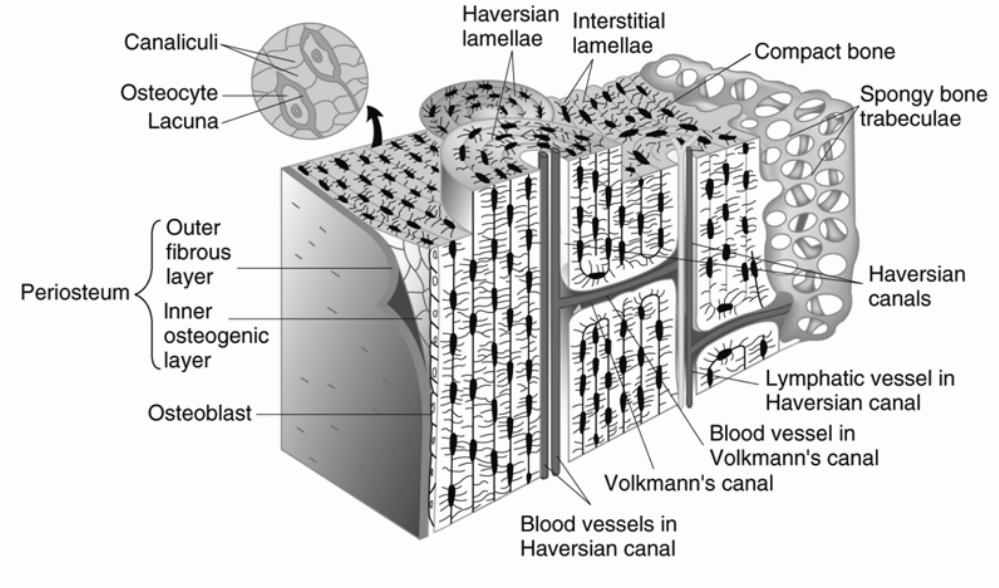

Figure 2.2: Diagram of a sector of the shaft of a long bone, showing cortical bone, trabecular bone, and various channels. (Tortora 1983).

2.3 Bone modelling and remodelling

Ossification and skeletal growth require two essential processes; bone modelling and remodelling. Bone modelling consists of changes in bone shape and size to allow growth and adaptation to mechanical loading (Seeman 2009). Bone may be added to or removed from the periosteal and endosteal surfaces. While all surfaces of the bone may be affected in remodelling, including the vascular cavities. In remodelling old bone is removed under the signal delivered by damaged osteocytes and replaced with the same amount of bone in the same site of previous removal (Seeman 2009). Therefore remodelling is a balanced process, that is bone resorption and bone formation must equilibrate to prevent dysfunctions otherwise seen in bone diseases, including osteoporosis (Robling and Turner

2009; Seeman 2009; Feng and McDonald 2011). The mechanical environment plays an essential role in the regulation of bone modelling and remodelling along with systemic regulators, especially hormones, whose homeostasis is greatly influenced by age and sexual maturity. Frost´s mechanostat theory (Frost 1987; Rittweger 2008) presents the relationship between bone formation, bone remodelling and the mechanical stimuli. This describes a window of mechanical usage which is considered physiological and maintains the bone in homeostasis. In the disuse window, the strains are below the physiological threshold, bone is resorbed by increased remodelling and in the overuse window, the strains exceed the upper boundary of the physiological domain, bone is formed by increased modelling. During space flight or prolonged bed rest bone mass is decreased due to absent or reduced mechanical stimuli (Lang et al. 2004).

2.4 Osteoporosis

Osteoporosis can be defined as a bone disease in which bone mineral density (BMD) is reduced, bone microarchitecture is disrupted and the amount and variety of non-collagenous proteins in bone is changed (Brunader and Shelton 2002). Trabecular bone becomes more brittle because of the miroarchitecture disruption and cortical bone becomes more porous and thinner. These changes lead to enhanced bone fragility and a consequent increase in fracture risk. Measurement of BMD is the basis of the diagnosis of osteoporosis. WHO classification of osteoporosis is based on DXA using the BMD of young women (20-30 years) as the reference value (T-score). Table 2.1 shows how the World Health Organization defines osteoporosis.

The underlying mechanism in all cases of osteoporosis is an imbalance between bone resorption and bone formation. Either bone resorption is excessive or bone formation is diminished. Bone remodeling is heavily influenced by nutritional and hormonal factors. Calcium and vitamin D are nutrients required for normal bone growth. Calcitonin, estrogen and testosterone increase osteoblast activity and therefore cause bone growth. The loss of estrogen following menopause causes a phase of rapid bone loss (Stevens and Lowe 1997; Cowin 2009).

Table 2.1: World Health Organization's criteria for defining bone density. SD is standard deviation and BMD is bone mineral density (Brunader and Shelton 2002).

Condition	Description
Normal	BMD value within 1 SD of the young adult reference mean
Osteopenia	BMD value of more than 1 SD below the young adult mean but less than 2.5 SD below this value
Osteoporosis	BMD value is 2.5 SD or more below the adult mean value
Severe osteoporosis	BMD value is 2.5 SD or more below the adult mean value in presence of one or more fragility fractures

Similarly, testosterone levels in men diminish with advancing age and are related to male osteoporosis. The incidence is much higher in women than in men due to its hormonal component and less bone mass at peak age (Cowin 2009). In general, osteoporotic fractures in men begin to increase several years later than in women.

In old age, both cortical and trabecular bone become thinned and are therefore more fragile and more prone to fracture. Fracture of proximal femur is common in the elderly. Osteoporosis may also develop following disuse, for example in the leg bones of a wheelchair-bound person (Stevens and Lowe 1997).

Physical activity causes bone remodelling. People who remain physically active throughout life have a lower risk of osteoporosis (Guadalupe-Grau et al. 2009; Bonnet and Ferrari 2010). Physical activity has its greatest impact during adolescence, affecting peak bone mass the most. In adults, physical activity helps maintain the bone mass, and might increase it. However, excessive exercise can lead to constant damages of the bone.

Osteoporosis causes a loss of strength and the risk of fractures increases dramatically. Osteoporotic fractures are those that occur under small stresses that would normally not lead to fractures in nonosteoporotic people. Common osteoporotic fracture sites include the vertebrae, the hip, the distal radius of the forearm, and the proximal humerus (Brunader and Shelton 2002; Cowin 2009).

Hip fracture is increasing worldwide due to rapidly aging populations (Kanis 1993). Lifetime risk of any osteoporotic fracture is very high and lies within the range of 40-50% in women and 13-22% for men (Johnell and Kanis 2005). Women are at a significantly higher risk for vertebral, forearm and hip fractures compared to men (Johnell and Kanis 2005). Hip fracture is a serious injury that can lead to permanent disability or mortality (Moyad 2003). Ambulation after a hip fracture is almost impossible until the fracture has been treated surgically, and 1 out of every 4 to 5 patients does not survive more than 1 year after the fracture (Moyad 2003; Johnell and Kanis 2005). In 90% of all hip fracture cases, a fracture is sustained through a fall (Schwartz et al. 1999; Korpelainen et al. 2006). Worldwide, the number of hip fractures has been estimated at 1.66 million in 1990 and is expected to increase to over 6.26 million in 2050 (Cooper et al. 1992). Hip fracture incidence rates are highest in northern Europe and the United States and lowest in Asia and Africa (Schwartz et al. 1999). In Iceland, lifetime risk of hip fracture at age 50 years and older is twice times higher in women than men. Ingimarsson et al. (Ingimarsson et al. 2004) studied the rates of proximal femur fractures among the Icelandic nation in the years 1984-2001 (Ingimarsson et al. 2004). 4506 proximal femur fractures were found in the study period, 73.8% females and 26.2% males. The total number of hip fractures was approximately between 250 to 300 per year for the last two decades. For females aged 60-64 the incidence lies round 167/100.000 but for age 90-94 at 4040/100.000. For males aged 60-64 the incidence was 65/100.000 and 1898/100.000 for the age group 90-94. For these reasons, researches helping to estimate the risk of hip fracture and prevent it are essential.

3 Bone strength

Bone is an anisotropic and inhomogeneous material that is a consequence of its varied composition and microstructure that differ across anatomic sites and are dependent of age (Rho et al. 1998; Jee 2001; Currey 2002). To understand why bones break, it is necessary to examine the factors that affect bone strength. Understanding the underlying mechanisms of age-related fractures may help to generate strategies for prevention and treatment. It has been generally accepted that osteoporosis manifests not only in reduced bone mass but also in altered bone quality. In this chapter, the factors that contribute to bone strength as well as the mechanical properties of both cortical and trabecular bone tissues are reviewed. In addition, age-related changes in bone strength are discussed.

3.1 Introduction

From an engineering point of view fractures result from a catastrophic structural failure of the bone, that is likely initiated at the material level, whereby the load applied to the bone exceed its load-bearing capacity. Bone has a number of mechanical properties and they can be described by a load-deformation curve (Fig 3.1) and stress-strain curve. It is important to distinguish between the mechanical behaviour of a whole bone as a structure (structural behaviour) and the mechanical behaviour of the bone tissue (material behaviour). The load-deformation curve (Fig 3.1) describes the relationship between load applied to a structure and deformation in response to the load and reflects the structural behaviour of the bone. Thus, the shape of this curve depends on both morphology and the material properties of the structure. The slope of the elastic region of the load-deformation curve represents the extrinsic stiffness of rigidity of the structure. Several other biomechanical properties can be derived including ultimate load (failure load); work to failure (area under the load-deformation curve), and ultimate deformation.

The stress-strain curve is analogous to the load-deformation curve but reflects the material behaviour of the bone that is independent of the geometry of the test specimen from which the properties were measured and it reflects the intrinsic properties of the material. The slope of the stress-strain curve within the elastic region is called the elastic or Young's modulus that is a measure of the intrinsic stiffness of the material. The values of stress and strain at the ultimate point are ultimate stress and ultimate strain. The area under the stress-strain curve is a measure of the amount of energy needed to cause a fracture and is a measure of the toughness of the specimen. The elastic region and the plastic strain region of the stress-strain curve are separated by the yield point. Before the yield point, the bone is considered to be in the elastic region, and if unloaded, would return to its original shape with no residual deformation. In the post-yield region the stresses begin to cause permanent damage to bone structure. Post-yield strains represent permanent deformations of bone structure caused by slip at cement lines, trabecular microfracture, crack growth, or combinations of these.

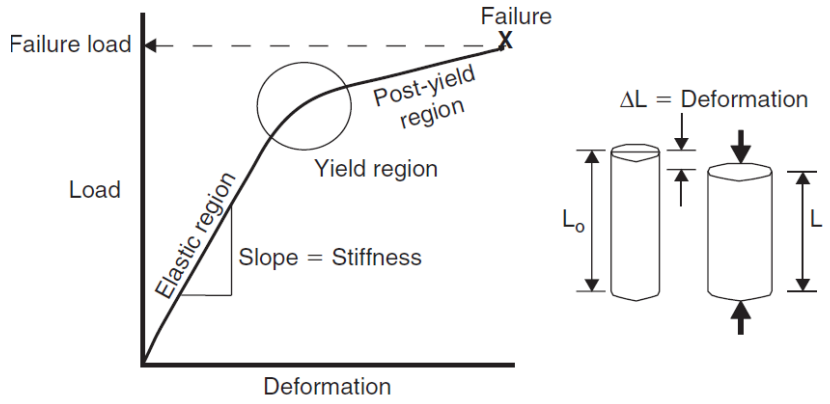

Figure 3.1: The load-deformation curve, illustrating the structural behaviour of a specimen. The slope of the curve in the elastic region defines the structural stiffness of the bone. In the post-yield region, the bone will undergo permanent deformations that will remain after the load is removed. During loading, the work done by the load is equal to the area below the curve. (Morgan and Bouxsein 2008). (With permission from Elsevier)

3.2 The Components that contribute to bone strength

Bone is a geometrically complex, composite material characterized by an array of mechanical properties (Currey 2003). The mechanical behaviour of a whole bone depends on the morphology of the bone as well as the intrinsic properties of the bone material itself. Thus, properties at the cellular, matrix, microarchitectural and macroarchitectural levels may all impact bone mechanical properties. Below the factors that are most likely to influence the resistance to fracture are listed:

The factors that contribute to bone strength (Felsenberg and Boonen 2005; Bouxsein and Seeman 2009):

Bone morphology
- Size
- Shape (distribution of bone mass)
- Microarchitecture (trabecular architecture, cortical porosity/thickness)

Bone tissue material properties
- Density, degree of mineralization, extent of microdamage, collagen traits

Bone turnover (Bone remodelling)

Role of bone geometry

The size of bone appears to have an effect on overall fragility (Silva and Gibson 1997) as well as the distribution of bone mass (Crabtree et al. 2001; Bouxsein and Seeman 2009). Resistance to bending and torsional loading is particularly important because the highest stresses in the appendicular skeleton are due to these loading modes (Martin 1993). The most efficient design for resisting bending and torsional loads involves distributing the bone mass far from the neutral axis of bending or torsion.

Role of microarchitecture

The microarchitecture of bone is an important structural property and that has been supported by experimental and clinical studies showing altered trabecular and cortical microarchitecture in subjects with fragility fractures compared to age-matched controls without fractures (Aaron et al. 2000; Bell et al. 2000; Ciarelli et al. 2000; Legrand et al. 2000; Link et al. 2000; Crabtree et al. 2001; Fields et al. 2009; Thomas et al. 2009). Microarchitecture can be understood as the structure of the trabecular bone, that is as the number and orientation of the trabeculae, the thickness of trabecular plates and rods, spacing of the trabeculae as well as the extent to which the trabeculae are interconnected and the structure of cortical bone, such as cortical thickness and porosity.

Role of material properties

Bone material properties, which are often determined by the degree of mineralization, characteristics of the collagen and extent of microdamge, are all important for bone strength (Ottani et al. 2001; Burr 2003; Follet et al. 2004). The stiffness and strength of bone are positively related to the degree of matrix mineralization (Follet et al. 2004). Collagen provides bone ductility and toughness (Currey 2003). Burr (Burr 2003) hypothesized that accumulation of microdamage in vivo may contribute to the increased fragility of the aging skeleton.

Role of bone turnover

Bone is a complex living tissue that undergoes constant renewal to repair and adapt to a mechanical loading in a healthy individual. The function of bone modelling and remodelling then influences the factors that determine whole bone strength, that is, bone geometry (shape and size), morphology and material properties.

3.3 Mechanical properties of bone

Bone is an anisotropic material that is its mechanical properties are dependent upon direction of loading, leading in general to greater compressive strength than tensile strength. Bone exhibits viscoelastic behaviour, the elastic modulus and the strength of the bone are dependent on strain rate (Bartel et al. 2006). Bone stiffness increases with increasing strain rate but ductility decreases with increasing strain rate (Bartel et al. 2006). Material properties of bone, particularly stiffness and strength, are strongly dependent on the volume fraction and density. There is a wider variation in density for trabecular bone than cortical bone that results in a much greater heterogeneity in trabecular bone's material properties compared with cortical bone. Cortical bone can withstand much greater load than trabecular bone but will not deform much before failure. In contrast, trabecular bone can deform significantly, but will fail at a much lower load.

3.3.1 Cortical bone

Human cortical bone is generally assumed to be transversely isotropic, that is it has one primary material axis (the longitudinal direction) and is isotropic in the plane perpendicular to the axis. The longitudinal axis is aligned with the diaphyseal axis of long

bones. Cortical bone is both stronger and stiffer when loaded in the longitudinal direction compared with transverse plane because of the nature of the arrangement of the osteons (Figure 3.2). Unlike the ultimate stresses, which are higher in compression, ultimate strains are higher in tension for longitudinal loading. In contrast to its longitudinal tensile behaviour, cortical bone is relatively brittle in tension for transverse loading and brittle in compression for all loading directions. Cortical bone is weakest when loaded transversely in tension and is also weak in shear. The mechanical properties of cortical bone are heavily dependent on porosity and degree of mineralization. More than 80% of the variation in the elastic modulus of cortical bone can be explained by a power-law relationship, matrix mineralization and porosity as explanatory variables (Currey 1990). Cortical porosity can vary from less than 5% to 30% and is positively correlated with age. Both elastic modulus and ultimate stress can be reduced by 50% percent when porosity is increased from 5% to 30% (McCalden et al. 1993). Thus, cortical bone properties for specific individuals depend on porosity.

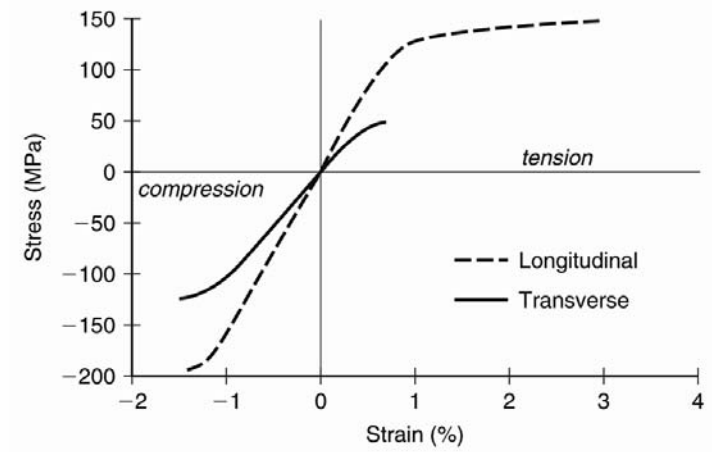

Figure 3.2: Typical stress-strain behavior for human cortical bone (Bartel et al. 2006).

3.3.2 Trabecular bone

Trabecular bone is a highly heterogeneous material, elastic modulus can vary 100-fold even within the same metaphysis and with varying degree‘s of anisotropy (Keaveny and Hayes 1993). Therefore the mechanical properties of trabecular bone should be accompanied by specifications of factors such as anatomic site, loading direction and age. From biomechanical perspective, the most important microstructural parameter for trabecular bone is its apparent density since the properties are often defined as a function of apparent density. Power-law relationships with bone density as the explanatory variable explain 60% to 90% of the variation in the modulus and strength of trabecular bone (Keaveny and Hayes 1993; Hernandez et al. 2001; Morgan and Bouxsein 2008) (Figure 3.3). These power-law relationships indicate that small changes in apparent density can lead to dramatic changes in mechanical behaviour. Even though trabecular bone can not withstand high load, it is however important as stiffening the structure by holding together the shell, prevent buckling, support cortical bone in case of impact loads and distributes loads at extremities.

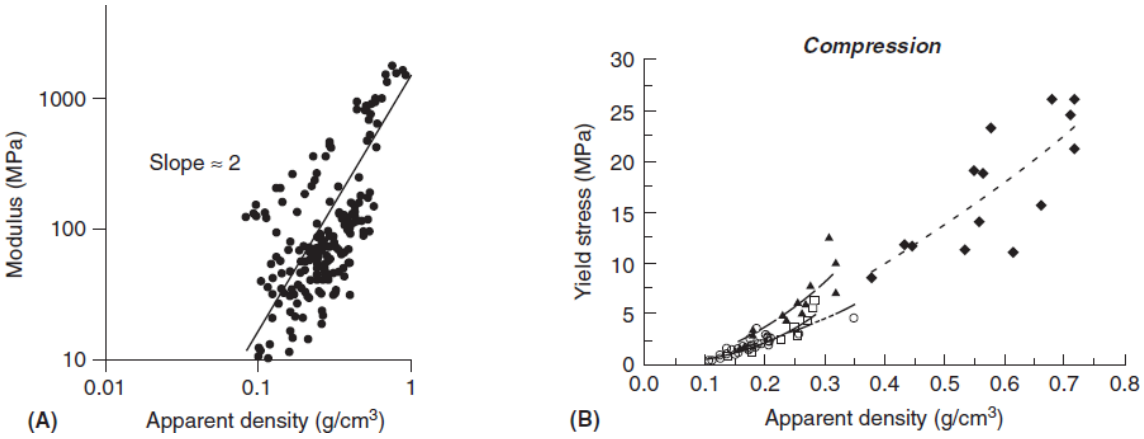

Figure 3.3: (A) Elastic modulus as a function of apparent density for trabecular specimens from a wide variety of species and anatomic sites. (Keaveny and Hayes 1993; Morgan and Bouxsein 2008) (B) Compressive yield stress as a function of apparent density for human trabecular bone speceimens from multiple anatomic sties. In general, the dependence of yield stress on density is different for different anatomic sites, although the exponents of the power-law relationships are approximately two. (Keaveny et al. 2001; Morgan and Bouxsein 2008). (With permission from Elsevier)

3.4 Age-related changes in bone strength

Human bone mass increases during growth, plateaus in young adults and between 30-35 years it begins to decrease (Figure 3.4). Bone is lost from all parts of the skeleton with advancing age but to a different degree. The loss of bone begins approximately 10 years earlier and proceeds about twice as fast in women than men. The onset of menopause is associated with increased bone turnover rate and an increase in bone loss because of the cessation of estrogen production (Riggs et al. 1998). Estrogen deficiency increases the lifespan of osteoclasts so that more bone is resorbed than is formed. The increased number of resorption cavities and the deeper resorption lacunae result in the net loss of trabecular connectivity, which deteriorate the trabecular architecture and lead to a decrease in the overall bone strength (Mosekilde 1990). There is evidence that estrogen also play a role in maintaining bone mass in men (Orwell 1999). Serum estradiol levels in older men correlated closely with bone mass but it is controversial whether male hormone levels are causally related to bone loss in elderly men but reduced testosterone levels can decrease muscle mass and indirectly affect bone mass.

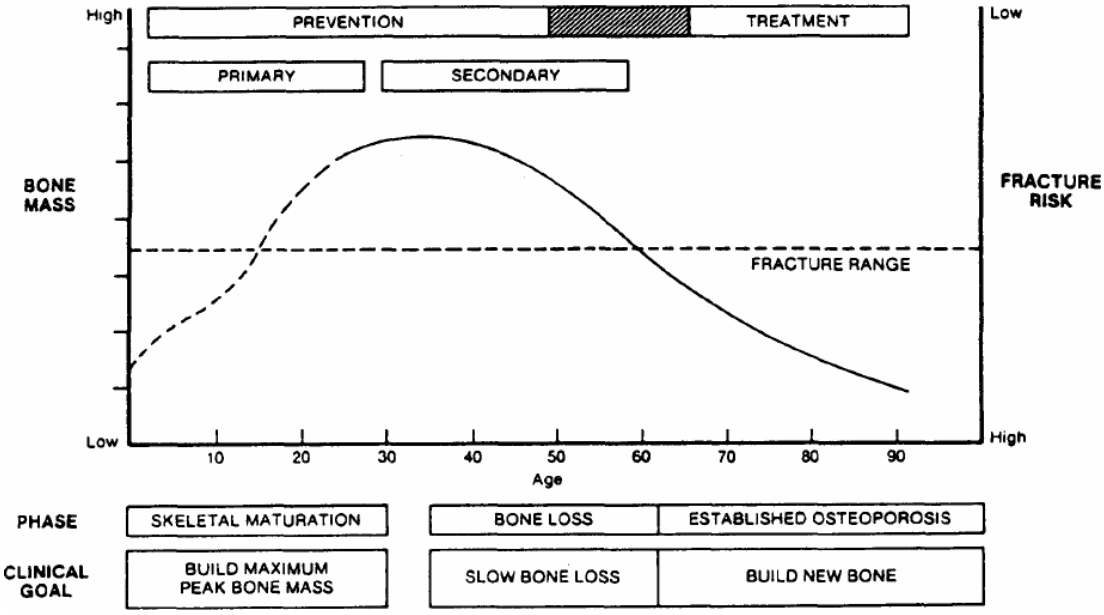

Figure 3.4: Diagram illustrating the process of bone gain and loss throughout life and fracture risk. Horizontal dotted line represents level which structural failures or fractures are likely to occur. This level is reached earlier in women than men because of the differences in the age-related bone loss. (Favus 1999)

The ability of cortical bone to resist fracture deteriorates with aging in both men and women. Several studies have indicated that while elastic modulus of cortical bone decreases modestly with aging, the strength and especially the toughness decrease more substantially (Currey 1969; Burstein et al. 1976; McCalden et al. 1993; Zioupos and Currey 1998). In human cortical bone from the femoral mid-diaphysis, the tensile and compressive strengths decrease about 2% per decade (Burstein et al. 1976). While the toughness (energy to fracture) declines by 5-12% per decade, indicating that cortical bone becomes more brittle and less tough with increasing age (Burstein et al. 1976; McCalden et al. 1993; Zioupos and Currey 1998). These changes in the mechanical properties of cortical bone are mainly caused by the increase in porosity with age (McCalden et al. 1993; Nishiyama et al. 2010; Zebaze et al. 2010; Macdonald et al. 2011). Other additional possible causes of the age-related deterioration of bone strength include changes in mineral crystal and collagen (Vashishth et al. 2001; Wang et al. 2002; Zizak et al. 2003). It is controversial that the mineralization of the matrix increases with increasing age (Grynpas 1993; Roschger et al. 2003; Roschger et al. 2008).

The elastic modulus and ultimate strength of trabecular bone decrease with age in both men and women as a consequence of markedly decrease in the apparent density (Mosekilde 1990; Ding et al. 1997; McCalden et al. 1997; Silva and Gibson 1997; Keaveny et al. 2001). The age-related reduction in strength of trabecular bone is not fully described by changes in density but is also reflected by deterioration in the trabecular architecture (trabeculae thinning, decrease in trabeculae number, increase in connectivity and separation) and in the mechanical properties of the trabecular tissue (Mosekilde 1990; Ding et al. 1997; McCalden et al. 1997; Silva and Gibson 1997; Hernandez et al. 2005; Fields et al. 2009).

The whole bone strength declines dramatically with age. When femoral neck was tested in a sideway fall configuration the older femurs were half the strength of the younger (Courtney et al. 1995) and older lumbar vertebral compressive strength was a quarter of the younger (Mosekilde 1998). In a population based study (QCT cohort 368 women, 320 men, age 20-97) it was shown that vertebral compressive strength reduces by 43% in women and 31% in men and showed earlier decline in women (Bouxsein et al. 2006). In another population based study (QCT cohort 362 women, 317 men age 21-90) it was shown that femoral strength declined heavily with age by 55% in women and 39% in men while femoral neck aBMD declined approximately half of the decline in whole bone strength (Keaveny et al. 2010).

Microdamage is another age-related change at both the cortical and trabecular tissue level which may contribute to bone strength. Microcracks appear to increase with age that decrease bone strength, especially resistance to fatigue fracture, (Burr et al. 1997) and may accumulate faster in women than men (Schaffler et al. 1995; Norman and Wang 1997) and accumulate more rapidly as bone mass decreases (Mori et al. 1997; Stepan et al. 2007).

With advancing age, the endocortical and intracortical remodelling increase resulting in that cortical bone becomes more porous and the cortex thinner (Poole et al. 2010; Zebaze et al. 2010). As endosteal bone loss proceeds the periosteal apposition takes place that is an adaptation to maintain whole bone strength, increasing the cross-sectional area of bone to reduce the load/unit area (stress) on the bone and increase its resistance to bending and torsion. Some studies indicate that men undergo the pattern of favourable geometric adaptation to a greater extent than women and that this may contribute to lower fracture rates in elderly men than women (Beck et al. 1993; Seeman 2001; Seeman 2002; Seeman 2003), whereas others have reported, in comparison with men that women exhibit similar perisosteal apposition (Riggs et al. 2004; Bouxsein et al. 2006; Sigurdsson et al. 2006). The discrepancy in findings related to sex-specific bone adaptation patterns may be because of differences in methodology, measurement site and that these studies used a cross-sectional design thereby possibly introducing secular trend.

4 Biomechanics of proximal end of femur fractures

A fracture occurs when loads applied to the bone exceed its strength therefore, to study the etiology of fractures it is important to consider both the factors that contribute to the loads applied to the bone as well as the bone strength (as was discussed in chapter 3). Since this dissertation is mainly focused on the structure of proximal femur and hip fractures, only events that are associated with hip fractures, loads that are applied to the hip during a fall and the load-bearing capacity of the proximal femur during that loading situation, are discussed in this section.

4.1 Fall and load applied to the proximal end of femur during a sideways fall

A fall is a critical event for hip fracture and fracture risk. It is estimated that more than 90% of all hip fractures in elderly are sustained through a fall (Grisso et al. 1991; Schwartz et al. 1999). However, fewer than 2% of falls results in a hip fracture (Nevitt and Cummings 1993; Michelson et al. 1995). Several studies have been conducted to characterize what kind of fall is a "high-risk" fall with regard to hip fracture (Hayes et al. 1993; Nevitt and Cummings 1993; Cumming and Kleinberg 1994; Greenspan et al. 1994; Greenspan et al. 1998). The direction of a fall is an important determinant of hip fracture occurrence (Hayes et al. 1993; Cumming and Kleinberg 1994; Greenspan et al. 1994; Greenspan et al. 1998; Kannus et al. 2006). During a fall, hip fracture risk is increased 6-fold by falling sideways instead of backward or forward (Robinovitch et al. 2003). Falling to the side and impacting the lateral aspect of pelvis or the side of the leg increased the risk of hip fracture by 20 to 30-fold relative to falling in any other direction (Hayes et al. 1993; Nevitt and Cummings 1993; Schwartz et al. 1998) and falling while turning was much more likely to lead to a hip fracture than falling when walking in one direction (Cumming and Kleinberg 1994). Other factors that are associated with risk for fracture are those that affect the potential energy content of a fall, such as fall height, body weight, trochanteric soft tissue thickness, muscle strength, neuromuscular control and protective response.

Laboratory studies have been conducted to explore the dynamics of sideways falls (Robinovitch et al. 1991; Robinovitch et al. 1995; van den Kroonenberg et al. 1995; van den Kroonenberg et al. 1996; Robinovitch et al. 1997a; Robinovitch et al. 1997b). In a study of the descent phase of sideways falls, six young healthy athletes (age 19-30) were asked to fall sideways, from two different configurations (standing still and walking slowly), onto a thick mattress and impact velocities and energies that occur during falls from standing height were estimated (van den Kroonenberg et al. 1996). The impact velocity was 7% lower when the participants did fall relaxed compared to falling naturally (that is with muscle activity). Only two subjects were able to break the fall with an outstretched arm and in both cases hip impact occurred first, followed by contact of arm or

hand. A considerable amount of the total available energy, about 70%, was dissipated during the descent phase of a sideways fall because of muscle activity and the stiffness and damping characteristics of the hip and knee joints. It is possible that the ability to dissipate energy during a fall decreases with advancing age, however it is suggested that age-related changes in forces due to a fall either a forward fall on outstretched hand or a sideway fall on hip are relatively small through life because the changes in height and weight are relatively small with age (Riggs et al. 2006). In a pelvis release experiment, 85 % of the total impact force, during a fall on the hip, is delivered along a compressive load path directly in line with the hip while only 15 % of the total impact force is distributed to structures peripheral to the hip. Forces are reduced by increasing trochanteric soft tissue. However this attenuation alone is insufficient to prevent hip fracture in a fall in which an elderly person lands directly on the hip because the peak forces directly applied to hip are well within the fracture range of elderly femur (Robinovitch et al. 1995). It has been shown that reduced trochanteric soft tissue thickness is associated with hip fracture in women but not in men (Nielson et al. 2009; Dufour et al. 2012; Hannan et al. 2012). In such falls, additional energy-absorbing mechanisms, such as breaking the fall with an outstretched hand and eccentric contraction of the quadriceps during descent, are likely to be involved.

4.2 Stress distribution within proximal end of femur

Many subsequent studies have investigated the stress distribution within the human femur (Lotz et al. 1995; Taylor et al. 1996; Duda et al. 1998; Simões et al. 2000; Van Rietbergen et al. 2003; Verhulp et al. 2008). Lotz et al. (Lotz et al. 1995) used a computer-based model to infer femoral load distribution during gait and falls in a normal and osteoporotic femur. A three-dimensional finite element model was generated based on a representative femur selected from a database of 80 femoral geometries. In all analyses they assumed linear and isotropic material behaviour. The osteoporotic femur model was geometrically identical but incorporated reduced material properties representative of the osteoporotic state. During gait, compressive stresses were concentrated at the base of the femoral neck and medial intertrochanteric region. In contrast, during impact from fall, large compressive stresses were developed in the region of the superior-posterior neck and posterior trochanteric region, the peak magnitude being 4.3 times that present during gait. While the distribution of stress for the osteoporotic femur was similar to the normal, the magnitude of peak stress was increased by between 33% and 45%. Another study was conducted by Verhulp et al. (Verhulp et al. 2008) where tissue stresses and strains were calculated with proximal femur micro-finite element models for a simulated fall to the side onto the greater trochanter. The meshes were created from high-resolution CT images of a healthy (T-score: -0.5) and a severely osteoporotic (T-score: -4.0) cadaveric proximal femur. In both femurs, the highest strains due to a fall occur in the cortex of the femoral neck and large compressive stresses were developed in the superior region (see Fig. 4.1). The cortical bone in the femoral neck was relatively highly loaded in the osteoporotic case (see Fig. 4.2).

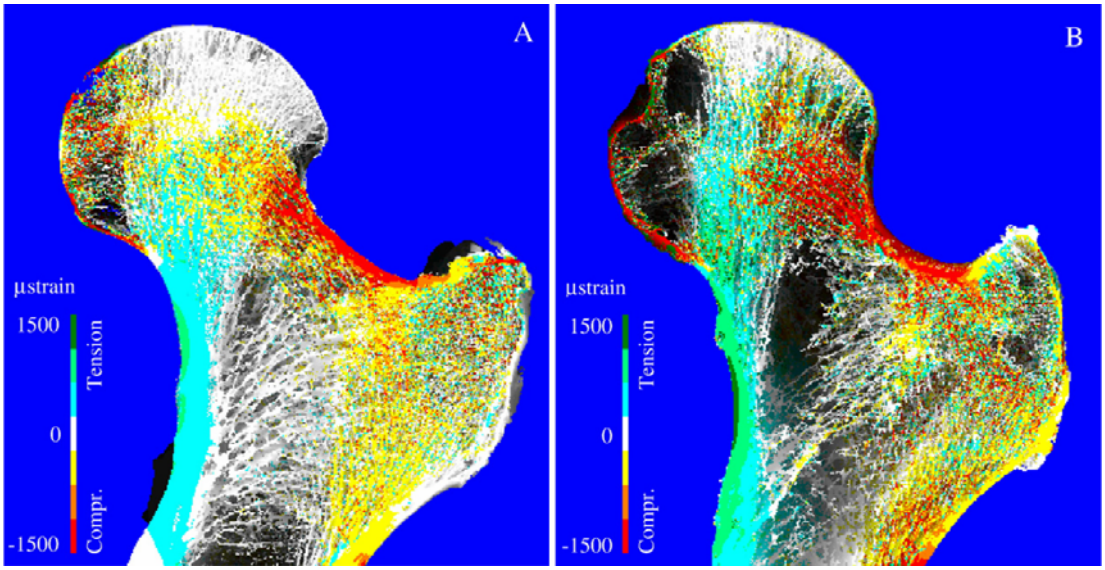

Figure 4.1: Maximal principal strain in a healthy (A) and osteoporotic (B) proximal femur during a simulated sideways fall onto the greater trochanter. The posterior halves are shown (Verhulp et al. 2008). (With permission from Elsevier)

The relative contribution of cortical and trabecular bone to fragility of the proximal femur has caused controversy, but much of this may be explained by different load configurations in mechanical testing. Lotz et al. (Lotz et al. 1995) suggested that the percentage of total load supported by cortical and trabecular bone was approximately constant for all load cases but differed depending on location. Cortical bone carried 30% of the load at the subcapital region 50% at the mid-neck, 96% at the base of the neck and 80% at the intertrochanteric region. Verhulp et al. (Verhulp et al. 2008) examined the load distribution in one healthy and one osteoporotic human proximal femur during a fall to the side with a much finer mesh. They suggested that the trabecular and cortical bone contributions to bone strength were similar but that the highest strains were located in the cortical shell. The trabecular compartment appeared minimally loaded in the osteoporotic femur viewed in an orthogonal plane to the neck axis. Manske et al. (Manske et al. 2009) suggested that both cortical and trabecular bone compartments contribute to proximal femur strength during a sideways fall and when they used a high threshold to differentiate cortical from trabecular bone, cortical bone contributed more to the variance in failure load than trabecular bone. The contribution of trabecular bone to bone strength in the femoral neck may be low during stance (Holzer et al. 2009) but Manske et al. studying cadaveric proximal femora by QCT reported that both cortical and trabecular bone contribute similarly to failure load (Manske et al. 2009). Trabecular bone is important in preventing buckling, but may be less important if the failure mechanism is crushing (Thomas et al. 2009). In a very recent experimental study the proximal femoral failure load in a sideways fall configuration was estimated by using CT-based bi-linear elastoplastic cortical bone FE model (Koivumäki et al. 2012a) and this model was slightly less accurate than a full bone FE model including trabecular bone (Koivumäki et al. 2012b). Their results suggest that cortical bone can largely explain the fracture load of a proximal femur during a sideways fall. As mentioned above the reason for this controversy might be explained by different methodologies but the relative contribution of cortical and trabecular bone to fragility might also be effected by age and severity of disease. The strength and stiffness of a bone

has been shown to be strongly correlated with bone volume fraction (Nazarian et al. 2008). Therefore it is likely that the contribution of cortical and trabecular can vary greatly with age and even between individuals.

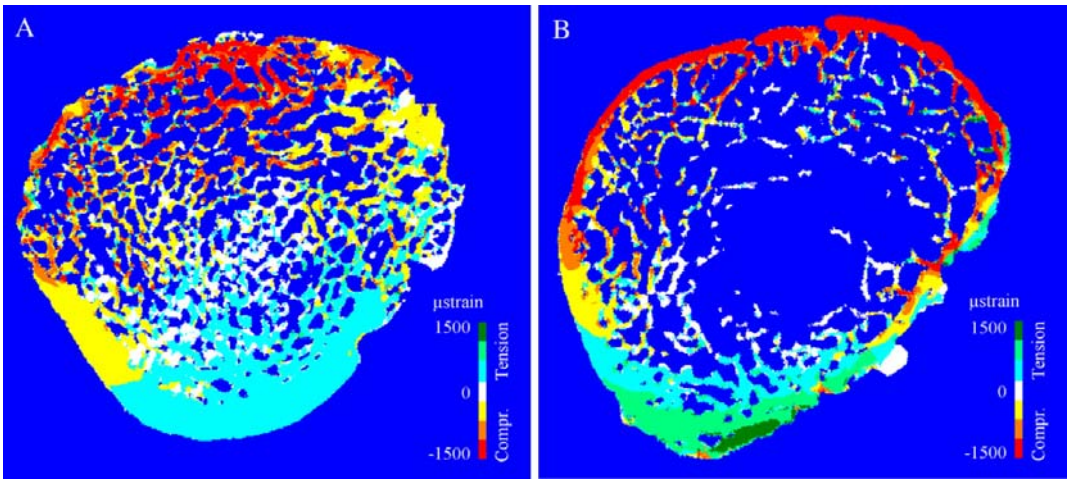

Figure 4.2: Maximal principal strain in the selected plane through the femoral neck in a healthy (A) and osteoporotic (B) femur during a simulated sideways fall onto the greater trochanter (Verhulp et al. 2008). (With permission from Elsevier)

4.3 Whole bone strength of proximal end of femur in vivo

The proximal femur is the subject of particular clinical interest, because the number of hip fractures is increasing worldwide due to rapidly aging populations (Kanis 1993) and leading to significant reductions in mobility, independence, and quality of life, and in some cases, increased mortality (Cooper et al. 1992; Cumming and Melton III 2002; Moyad 2003). As discussed previously, several factors contribute to the load-bearing capacity of a bone, including, its intrinsic material properties as well as the size and spatial distribution of the bone tissue. These factors of proximal femur have been widely studied both in vitro and in vivo.

Whole bone strength of proximal femur in vivo has been investigated using finite element analysis in population based studies (Orwoll et al. 2009; Keaveny et al. 2010; Keyak et al. 2011; Shreyasee et al. 2011; Lang et al. 2012; Srinivasan et al. 2012), this is the most technologically advanced method currently available for noninvasive clinical assessment of femoral strength. In a prospective fracture study of elderly men (MrOS; fracture cases, n=40 and controls, n=210), finite element derived femoral strength (HR = 6.5, 95% CI: 2.3–18.3) and load-to-strength ratio (HR = 4.3, 95% CI: 2.5–7.4), from baseline QCT scans in a lateral fall condition, were strongly associated with hip fracture risk when adjusted for age, BMI, and study site (Orwoll et al. 2009). When aBMD as measured by DXA for the total hip was accounted for, the load-to strength ratio remained a significant risk factor (HR = 3.1, 95% CI: 1.6–6.1). In additionally, all men who had FE-derived femoral strength values of less than 2900 N reported a new hip fracture during follow-up (n=13 or ~ 33% of total hip fractures). Interestingly, over half of those fracture cases were classified as having osteopenia rather than osteoporosis on the basis of their DXA derived

aBMD T-score. Van den Kroonenberg et al. (van den Kroonenberg et al. 1995) suggested using biomechanical models that peak impact forces delivered to the proximal femur during a sideways fall that peak impact forces applied to the greater trochanter ranged from 2900 to 4260 N. In contrast, a study showed that FE analysis of the proximal femur was comparable in determining the probability of prevalent overall and osteoporotic fractures to total hip aBMD (Shreyasee et al. 2011).

Another study was conducted to characterize the variations in femoral strength (virtually loaded to failure in simulation of an unprotected sideways fall with impact on the greater trochanter) across age in women and men (age-stratified cohort of 362 women and 317 men, aged 21-89 years) (Keaveny et al. 2010). The percent reductions over adulthood were about two-fold greater for femoral strength (-55% in women, -39% in men) than for femoral neck aBMD (-26% in women, -21% in men). The decline in strength started in the mid-40s for women and one decade later for men. In a longitudinal study using QCT data to compare changes in proximal femoral bone density, structure, and whole bone strength in men and women was recently published (Lang et al. 2012). The results showed that elderly men and women lose proximal femoral whole bone strength at a rate of 4–13% per five years, with women, on average showing twice the loss of strength as men in single-limb stance and posterolateral fall loading conditions. They also observed a clear dependence of age-related bone strength loss on loading condition, with stance strength decreasing at a 50% lower rate than fall strength. Cross-sectional data obtained from a QCT-scanned subset of the Rochester Epidemiology Study indicate that some of underlying reasons for reduction in femoral strength are related to a very significant decrease in total vBMD (-46% and -34% in women and men, respectively) and tBMD (-56% and -45% in women and men, respectively) as well as reduction in cortical vBMD (-24% and -13% in women and men, respectively) but the reductions were larger in women than men (Riggs et al. 2004). In both women and men the total area increased but there was no sex difference. In a cross-sectional analysis carried out in the AGES-Reykjavik cohort, Sigurdsson et al. reported that the gender difference in various measures of proximal femoral skeletal integrity, including cortical and trabecular vBMD and estimates of femoral neck axial compressive and bending strength, continued to increase in the elderly subjects, with women showing cross-sectional rates of bone density and estimated strength loss two–four times higher than those of men, depending on the specific measure (Sigurdsson et al. 2006).

In a nested age- and sex-matched case-control study in AGES Reykjavik cohort (women: fracture cases, n=77, controls, n=152; men: fracture cases, n=51, controls, n=97) FE derived strength for stance and posterolateral fall loading and total aBMD were estimated from QCT data (Keyak et al. 2011). They found that there were sex differences between the association of FE-derived femoral strength and hip fracture risk. However, their key finding was that incident hip fracture was associated with a greater decrement in FE strength between fracture cases versus controls in men than in women. Srinivasan et al. (Srinivasan et al. 2012) showed that men and women having matched values of femoral neck aBMD had quite similar measures of FE-derived femoral strength and even closer values of the load-to-strength ratio. In addition, the men were 6 years older than the women, had larger bone size and had lower vBMD. It should be noted that the FE studies that have been discussed do to some extent differ with respect to study design and FE methodology.

4.4 Whole bone strength of proximal end of femur ex vivo

The finite element analysis of QCT scans has been validated in cadaver studies (Silva and Gibson 1997; Cody et al. 1999; Keyak 2001; Keyak and Y 2003; Roberts et al. 2009). Several laboratory studies have evaluated the load-bearing capacity of the proximal femur by using a stance configuration (Keyak et al. 1998; Cody et al. 1999; Keyak 2001; Keyak and Y 2003; Bousson et al. 2006). Other studies have evaluated the load-bearing capacity of the proximal femur in a configuration designed to simulate a sideways fall with impact to the greater trochanter (Courtney et al. 1994; Bouxsein et al. 1995a; Bouxsein et al. 1995b; Courtney et al. 1995; Pinilla et al. 1996; Cheng et al. 1997; Keyak et al. 1998; Keyak 2001; Lochmuller et al. 2002; Bauer et al. 2006). The femoral failure loads were quite different between studies because of the loading direction. For example, Pinilla et al. (Pinilla et al. 1996) found that small differences in impact direction of a sideways fall influence the failure load of the proximal femur as much as 25 years of age-related bone loss.

4.5 Geometry of proximal end of femur

Several studies have confirmed that noninvasive assessments of bone geometry using DXA or QCT are correlated to the strength of the proximal femur. Femoral neck area, neck width, and neck axis length are all positively correlated with femoral failure loads (Bouxsein et al. 1995b; Courtney et al. 1995; Pinilla et al. 1996; Cheng et al. 1997; Huber et al. 2008). In cadaver studies, femoral bone mineral content and density were associated with femoral strength and explain between 40% and 80% of the variation in measured femoral strength (Bouxsein et al. 1995a; Cheng et al. 1997; Bouxsein et al. 1999; Cody et al. 1999; Bauer et al. 2006). There is strong evidence from prospective clinical studies that low BMD is a risk factor for hip fracture (Marshall et al. 1996; Bates et al. 2002; Johnell et al. 2005), however half of all hip fractures occur in persons in whom hip aBMD is not severely reduced (Stone et al. 2003; Schuit et al. 2004; Sornay-Rendu et al. 2005; Wainwright et al. 2005).

Human proximal femurs have thinner superior than inferior cortices at the mid-femoral neck region and there is marked further thinning in the superior regions with advancing age (Boyce and Bloebaum 1993; Crabtree et al. 2000; Mayhew et al. 2005; Poole et al. 2010). Maximal compressive strain from a sideways fall on to the greater trochanter occurs in the superior femoral neck (Lotz et al. 1995; Pinilla et al. 1996; Carpenter et al. 2005; Mayhew et al. 2005; Verhulp et al. 2008) with maximal tensile strain in the inferior cortex (Thomas et al. 2009). In load-to-failure testing, cadaveric femurs often fractured at the thin superior cortex (de Bakker et al. 2009) in a sideways fall simulation as predicted (Carpenter et al. 2005; Mayhew et al. 2005; Thomas et al. 2009). Very recently the trabecular bone micro-architecture of the femoral neck was studied in elderly women with and without a hip fracture (Milovanovic et al. 2012). The fracture cases had lower bone volume fraction, lower connectivity density and higher trabecular separation. Particularly, the superolateral region of the neck displayed substantial trabecular micro-architectural weakness in the elderly women who had sustained a femoral neck fracture.

Thin cortex at femoral neck has been reported as a risk for hip fracture (Rivadeneira et al. 2007; Black et al. 2008; Ito et al. 2010). Black et al (Black et al. 2008) examined the relationship between QCT-derived structural and densitometric measures of the proximal femur and hip fracture risk in men. They found that three QCT-derived femoral neck parameters including percent cortical volume, minimal cross-sectional area, and trabecular density were each associated with hip fracture risk. Femoral neck structural parameters (percent cortical volume and minimum cross-sectional area) continued to make independent contributions after adjustment for aBMD in their data. Rivadeneira et al (Rivadeneira et al. 2007) investiaged the relationship between DXA-derived hip structural and densitometric measurements and hip fracture risk in both men and women. Their findings suggested that extreme thinning of cortices in expanded bones plays a key role on local susceptibility to fracture. Bell et al (Bell et al. 1999b) quantitated the areas of cortical and trabecular bone within octants in 13 female intracapsular hip fracture cases and 19 cadaveric controls (9 males, 10 females). They concluded that loss of cortical, rather than trabecular, bone predominates in femoral neck fracture cases. This loss occurred primarily along the infero-anterior to supero-posterior axis which bears the greatest stress during a fall. Cortical bone porosity was also increased in the anterior region of the mid-cross-section of the femoral neck in cases of intracapsular hip fracture compared with age-matched cadaveric samples (Bell et al. 1999a).

5 Objectives

The principal aim of the study was to get a better insight into the pathomechanism of hip fracture and possibly improve the assessment of risk of hip fracture. QCT integral BMD in AGES cohort had shown similar fracture risk prediction but no better than DXA-like BMD (Siggeirsdottir et al. 2007). This gave further reason to study other possibilities of QCT in this respect.

The following chapter summarizes the main objectives of this project. Readers are referred to appended papers for a more detailed discussion.

5.1 Specific aim 1: Regional cortical thickness measurements at mid-femoral neck and hip fracture

In a prospective nested case-control study, the primary aim was to explore the utility of regional cortical measurements at the mid-femoral neck (using multi-slice computed tomography, CT) for predicting femoral neck and trochanteric fracture in elderly men and women. Using baseline CT scans of femoral neck and trochanteric fracture cases (n=143) and controls (n=298) from the population-based AGES-Reykjavik study, cortical thickness estimates in anatomical quadrants were made within a cross sectional region of interest of the mid-femoral neck, (orthogonal to the femoral neck axis).

5.2 Specific aim 2: Cortical thickness measurement at femoral shaft and thigh muscles and lower limb fractures

In a cross-sectional study, the purpose was to explore if the association between muscular and bone parameters in the mid-thigh differs by age and sex in older people using data from a single axial CT section through the mid-thigh. Furthermore, to study if those parameters are associated with incident low-trauma fractures in the lower limbs. A total of 3,762 older individuals (1,838 men and 1,924 women), aged 66– 96 years, participants in the AGES-Reykjavik study were studied during a median 5.3 years of follow-up.

5.3 Specific aim 3: Age-related changes of regional cortical thickness and BMD measurements at mid-femoral neck in elderly individuals using longitudinal QCT data

In a longitudinal study, our primary aim was to investigate, using multi slice computed tomography (CT), change over 5 years in regional cortical thickness and cortical and trabecular BMD measured separately. We also assessed integral (i.e., cortical plus trabecular) BMD and simulated-DXA-like changes at this location. The study cohort consisted of 100 men and 300 women aged 66-90 years from the population-based AGES-Reykjavik study with available two hip QCT-scans with 5 years apart. All participants were drug-free, that is not using medications known to affect bone mineral density. Segmental QCT analysis of the mid-femoral neck was applied to estimate cortical thickness and BMD measurements in the supero-lateral (superior) and infero-medial (inferior) regions of the mid-neck.

6 Methods and materials

The following chapter describe the methods used for carrying out each of the objectives in chapter 5. Appended papers provide further discussion on applied methodologies.

All individuals included in the three study series were participants in the Age Gene/Environment Susceptibility-Reykjavik Study (AGES-REYKJAVIK), a single-center population study of Icelandic men and women. Design and recruitment of the AGES study have been described in details (Sigurdsson et al. 2006; Harris et al. 2007). All participants provided written informed consent, and the study was approved (VSN 00-063) by the National Bioethics Committee in Iceland as well as the Institutional Review Board of the Intramural Research Program of the National Institute of Aging.

6.1 Paper I – A prospective nested case-control study

Study participants

In this study 143 (88 women and 55 men) hip fracture cases and 298 (187 women and 111 men) controls were included. The controls were matched for calender year of recruitment, sex and age to each fracture case. Medical records were checked biannually from all hospitals receiving hip fractures in Iceland. From these records, we identified all low trauma fractures, defined as a fracture resulting from a fall from a standing position or lower. All reported fractures were categorized into femoral neck fracture and trochanteric fracture (using the ICD 10 classification).

QCT measurements

CT measurements were performed in the hip and CT Hounsfield units calibrated to equivalent bone mineral concentration. The CT images were processed to extract measures of volumetric BMD (vBMD), areal BMD (aBMD, DXA equivalent) and bone structure at the femoral neck using QCT PRO CTXA software (Mindways, Austin, Texas).

A scripting command was written to extract automatically six contiguous cross-sectional slices of 1 mm thickness of the mid-femoral neck from a reproducible location for measurements, was used with the QCT PRO Bone Investigational Toolkit (BIT2) software (Mindways, Austin, Texas). Estimated cortical thickness (Est CTh) at the mid-femoral neck was determined in anatomical quadrants (see Fig 6.1). The centre of area was the internal reference point, with 16 equal sectors defined by equal angles (22.5°) and the first sector boundary defined by a vertical line; see Fig. 6.1. This resulted in four anatomical quadrants (Fig. 1); supero-anterior (SA: from sectors 2, 3, 4, 5), infero-anterior (IA: 6, 7, 8, 9), infero-posterior (IP: 10, 11, 12, 13) and supero-posterior (SP: 14, 15, 16, 1). The cortical bone threshold was chosen at 450mg/cm^3 because this minimized differences from cortical thickness estimates made by higher resolution CT and histological methods (Poole

et al. 2010; Treece et al. 2010). Est CTh was calculated for each of the 16 sectors as follows; the cortical area was measured automatically (by pixel counting) on each cross-sectional image. In each sector, the cortical bone mass was assumed to be evenly distributed between the two surface boundaries (one periosteal and the other endosteal). The boundaries were approximated as concentric arcs of constant curvature, which enclosed the point of the cortical centre of mass. Est CTh by quadrants was averaged across corresponding sectors and the data from the 6 cross-sections were used to derive a single mean estimate for each quadrant. Average CTh (AvgCTh) was evaluated as the mean across the four quadrants.

Single mean integral volumetric BMD (IntvBMD) estimate was made from the 6 cross-sections in the mid-femoral neck. DXA-equivalent for the total femoral neck aBMD (FN aBMD) was determined by the software and hip axis length (HAL) was measured from 2D projection screen images using the QCT PRO slice-pick measurement tool.

Statistical analyses

One-way analysis of variance (ANOVA) was used to compare variables among controls, FN cases, and TR cases. Repeated measures MANOVA were used to determine the differences and parallelism between controls and cases across the quadrants. Student's t-test was used to test for female-male differences. The percent differences between cases and controls in Est CTh by quadrants and FN aBMD were estimated using linear regression on the log-transfromed data. General linear models were used to estimate percent changes over a 10-years age interval having the outcomes (CTh) on log-scale; then exponentiating the regression parameter (slope) for age generates the percent change in 1-year. The correlation coefficient between two quadrants was estimated assuming unstructured covariance structure using a mixed model. The analysis of time to low trauma hip fracture was performed using the Cox proportional hazards regression model and results were expressed as hazard ratios (HRs; and 95%CIs) per 1 SD change in the parameters. All analyses were adjusted for age, weight and height. Stepwise selection methods were used in the multiple predictor proportional hazard models to examine interdependence of CTh by quadrants and total femoral neck aBMD.Women and men were analyzed separately, as were femoral neck and trochanteric fracture cases. The programs Matlab 7.6 (R2008a) (MathWorks Inc., Natick, Massachusetts, USA) and SAS 9.2 (SAS Institute Inc, Cary, North Carolina, USA) were used for statistical analyses.

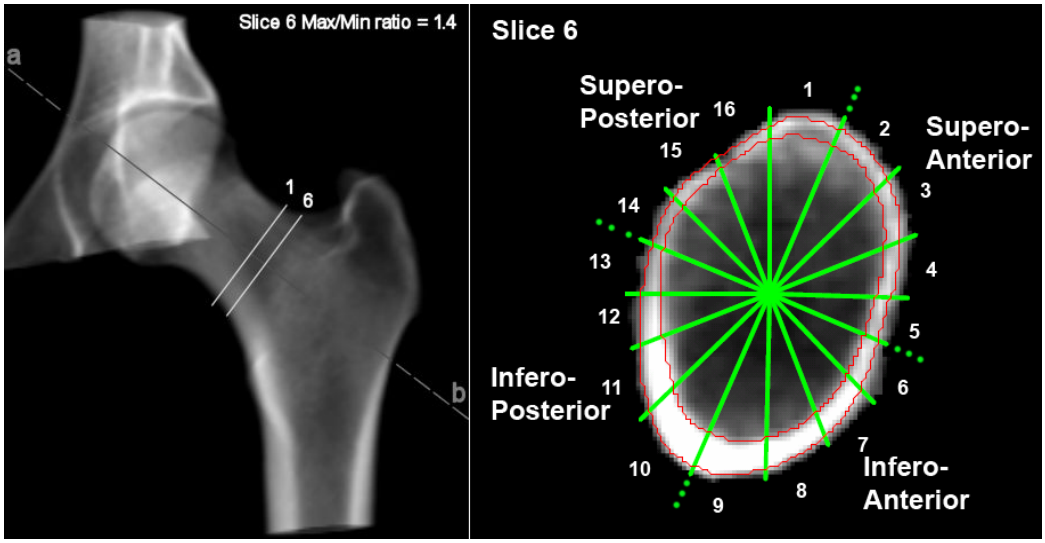

Figure 6.1: 3D CT rendering (left) showing ROIs and Slice Position. Shape of FN at max/min ratio 1.4 (right) showing anatomical quadrants (note the clockwise shift of one sector due to sagittal positioning). The red contours show the cortex.

6.2 Paper II - A cross-sectional study

Study Participants

The study cohort consisted of 3,762 older individuals (1,838 men and 1,924 women) aged 66-96 years and all participants were drug-free, that is not using medications known to affect bone mineral density. Medical records were checked biannually from all hospitals receiving fractures in Iceland. From these records, all incident low-trauma lower limb fractures were identified, defined as a fracture resulting from a fall from a standing position or lower. Fractures were categorized as being at the hip (S72.0–S72.2), femoral shaft (S72.3), lower leg (S82.1–S82.4), and ankle (S82.5–S82.9). The median follow-up time was 5.3 years. Of those who were analysed, 113 women and 66 men sustained incident low trauma lower limb fracture during follow-up.

CT measurements and maximal isometric knee extension strength

CT measurements were performed at the mid-thigh and a single axial section through the mid-thigh was processed to extract measures of bone and muscle variables in the mid-thigh. We estimated total shaft area (cm^2), medullary area (MA) (cm^2), cortical area (cm^2), cortical thickness (cm), buckling ratio (BR), and muscular area (cm^2). An operator used a manual contouring program to draw the contours of the hamstring, sartorius, and quadriceps muscles of the thigh; and total muscular cross-sectional area was calculated.

Muscle strength was assessed as the maximal isometric strength of the leg while the individual was sitting in an adjustable dynamometer chair (Good Strength; Metitur, Palokka, Finaland). The seat belt was fastened in the pelvic area to prevent movement of the body during the test, and the ankle was fastened by a belt to a strain-gauge transducer. Knee extension strength was measured at a knee angle of 60° from full extension toward flexion. Three maximal efforts, separated by 30 s of rest, were conducted. During the

measurements, individuals were encouraged verbally to produce at their maximal capability, and the highest value was used.

Statistical analyses

General linear models were used to estimate the association with age and mean values of variables adjusted to age 75 years. Current height and weight were used to correct for body size. Correlations between height and weight were r = 0.31 and r = 0.48 in women and men, respectively (both $p<0.001$). Estimates were obtained using linear combinations of regression parameters with an intercept, age set at 75 years, height at 175 cm for men and 161 cm for women, weight at 83 kg for men and 71 kg for women. To estimate percent variances per 10 years in age interval, outcomes were analyzed on a natural log scale. Then, the regression parameter (slope) for age can be interpreted as a percent change for 1 year difference. This effect was then scaled to represent the effect of 10 years. One-way analysis of variance (ANOVA) was used to compare men and women. Associations between variables were estimated by Pearson's correlations, and partial correlations were estimated from linear regression. In Fig. 2 the adjusted values for cortical area and muscular area were estimated from a regression model. In a regression model, cortical area and muscular area were the outcomes and age, height, and weight were the parameters (subtracted from the mean in each parameter). Adjusted values were estimated as the residuals from the regression model and scaled with the intercept. ANOVA was used to compare fracture cases and controls. The Cox proportional hazards regression model was used to estimate risk of fracture, using time from visit to the AGES-Reykjavik study as the time scale, with adjustment for age, height, and weight at entry. Analyzes were performed for men and women separately. The program R 2.9.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses.

6.3 Paper III – A longitudinal study

Study participants

A subset of 400 (100 men and 300 women) individuals were randomly chosen for detailed quantitative analysis from the AGES cohort who had two QCT scans of the hip, had not sustained a hip fracture and not using medications known to affect bone density. The median follow-up time was 5.1 years.

QCT measurements

CT measurements were performed in the hip and CT Hounsfield units calibrated to equivalent bone mineral concentration. The CT images were processed to extract measures of volumetric BMD (vBMD), areal BMD (aBMD, DXA equivalent) and bone structure at the femoral neck using QCT PRO CTXA software (Mindways, Austin, Texas) using the same protocol as in paper I.

A scripting command, written to extract automatically six contiguous cross-sectional slices of 1 mm thickness of the mid-femoral neck from a reproducible location for measurements, was used with the QCT PRO Bone Investigational Toolkit (BIT2) software (Mindways, Austin, Texas). Estimated cortical thickness (Est CTh) at the mid-femoral neck was determined in two anatomical surfaces. This resulted in two anatomical regions (Fig. 6.2): the superior surface (S: from sectors 14, 15, 16, 1, 2, 3, 4, 5), and the inferior surface (I: 6,

7, 8, 9, 10, 11, 12, 13). Est CTh by superior and inferior surfaces was averaged across corresponding sectors and the data from the 6 cross-sections were used to derive a single mean estimate for each region. The integral vBMD (IntvBMD), cortical vBMD (CortvBMD) and trabecular vBMD (TrabvBMD) values for the superior and inferior regions were averaged across corresponding sectors and the data from the 6 cross-sections were used to derive a single mean estimate for each region. The mean integral BMD estimate for the mid-femoral neck (FN IntvBMD) was also estimated. The mean cross-sectional area (CSA) of the mid-femoral neck was estimated from the 6 cross-sections and defined as the area enclosed by an external bone perimeter. DXA-equivalent for the total femoral neck aBMD (FN aBMD) was determined by the software.

Statistical analyses

Since we aimed to measure rates of loss or gain of our measured variables in units of measurement and also to compare rates of change between regions with considerably different mean values, as well as between the two sexes, we performed linear regression analysis both on the untransformed and on natural log-transformed data. Random effects regression models were used to determine the average amount of change in study parameters during follow-up for each participant. Random effects models account for between-subject variation and within-subject correlations between repeated measurements. Thus each participant had a subject-specific intercept and slope. Time was modelled as time between the two measurements. Fixed effect included the mean age of baseline age and follow-up age. Change is reported as the absolute change and percent change. The significance difference between sexes was tested with interaction between sex and time in the models. The effect of baseline height, baseline weight and weight change during follow-up was tested by adjusting for each variable separately in the models and with interaction with time and that did not affect the estimated average changes (results not shown).

A participant was considered to have maintained or increased in CtTh and BMD during follow-up if the difference between follow-up and baseline measurement was ≥ 0. Student's t-test was used to test for difference between those who maintained or increased and those who lost bone. Mean inferior CtTh across the weight change quartiles is reported graphically and the difference by quartiles was analyzed by one-way analysis of variance (ANOVA). The baseline and follow-up measurements for S CtTh, I CtTh and FN vBMD for each individual's visits were plotted to provide a graphical representation of the variability in the loss. The partial correlation coefficients were estimated from linear regression. The programs R 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.2 (SAS Institute Inc, Cary, North Carolina, USA) were used for statistical analyses.

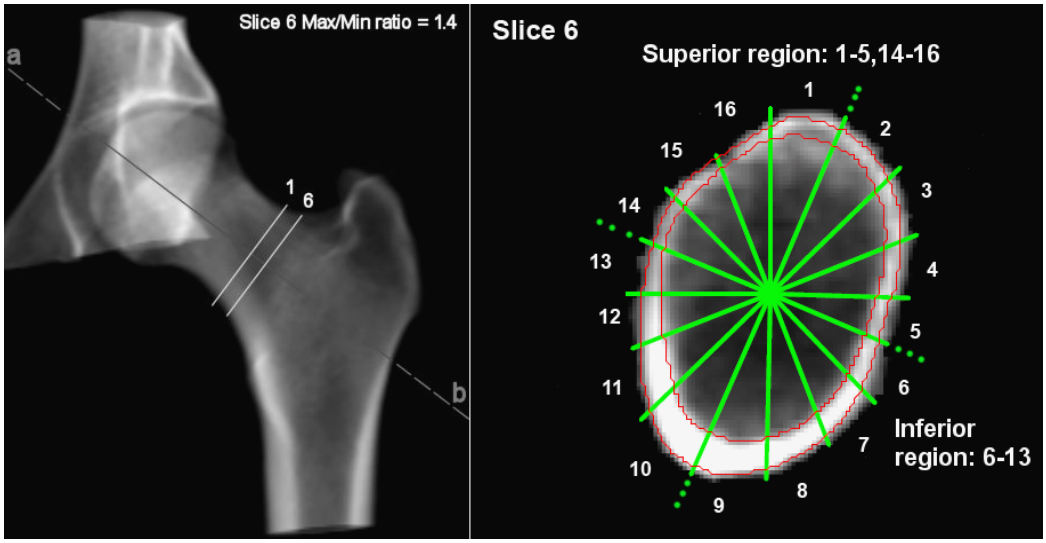

Figure 6.2: 3D CT rendering (left) showing ROIs and Slice Position. Shape of FN at max/min ratio 1.4 (right) showing the superior and inferior region (note the clockwise shift of one sector due to sagittal positioning). The red contours show the cortex.

7 Summary of key results

The following chapter summarizes the key findings. Appended papers provide further discussion on the results of this study series.

7.1 Distribution of cortical bone in the mid-femoral neck and hip fracture (Paper I)

In a prospective nested case-control study a segmental QCT analysis of the mid-femoral neck was applied to explore the utility of cortical thickness in different regions for predicting incident femoral neck and trochanteric fracture in elderly men and women. The supero-lateral region of the femoral neck was a stronger predictor for hip fracture than the infero-medial region, particularly in men. There were significant gender differences in Est CTh measurements in the control group but not in the case group. The CTh estimated in the supero-anterior quadrant was the best discriminator of cases (n=143) and controls (n=298). In multivariable analysis for risk of FN fracture, Est CTh in the SA quadrant was significant in both women and men, and remained a significant predictor after adjustment for FN areal BMD (DXA-like), ($p=0.05$ and $p<0.0001$, respectively). In conclusion, the results suggest that cortical thinning superiorly in the hip might be of importance in determining resistance to fracture.

Research Highlight

- Cortical thickness in the supero-anterior quadrant best predicted hip fracture.
- There was no significant difference in CTh in the fracture group between sexes.
- Majority of elderly women and minority of men have a critical thinned superior cortex.
- Thin supero-lateral cortex is a stronger risk factor than the infero-medial in mid-femoral neck.

7.2 Mid-thigh cortical bone structural parameters, muscle mass and strength, and association with lower limb fractures (Paper II)

In a cross-sectional study we explored if the association between muscular and bone parameters in the mid-thigh differs by age and sex in a total of 3,762 older individuals (1,838 men and 1,924 women), aged 66–96 years. Additionally, we studied the association of these variables with incident low-trauma lower limb fractures. The results showed that the size of the medullary area (MA) and the consequent thinning of the cortex with higher buckling ratio (BR) were significantly associated with lower limb fractures in both sexes. These bone parameters varied differently with age by gender, the increment in MA and BR with age was almost fourfold greater in women than men. The bone parameters most strongly associated with fractures were, however, mostly independent of baseline muscular parameters. The muscle parameters correlated most strongly with cortical area and total shaft area (adjusted for age, height, and weight) but explained less than 10 % of variability in those bone parameters. The total cross-sectional muscular area and knee extensor strength declined with age similarly in both sexes. The muscle parameters were protective against incident lower limb fractures in both sexes. The results showed that bone and muscle loss proceed at different rates and with different gender patterns. The study supports the idea that periosteal apposition is insufficient to protect bone strength against the medullary expansion due to endocortical resorption. This is consistent with a higher rate of fracture in women as the two genders show no change in total shaft area but women have a larger increment in MA. Thus, our results support the notion that endocortical resorption may be a key process for the development of bone fragility in lower limbs in old age. Better understanding of the determinants of endocortical resorption might thus be of importance in the prevention of low-trauma lower limb fractures in older people.

Research Highlight

- Bone and muscle parameters show a weaker association in older people than has been described in younger people (Bass 2000; Schoenau et al. 2000; Matthews et al. 2006).

- Large medullary area, low cortical thickness, and high buckling ratio were significantly associated with fractures in both sexes.

- The muscular area and strength seem to be of importance for protection against incident lower limb fractures in both sexes, and this seems to be mostly independent of bone parameters.

7.3 Age-related regional losses of cortical and trabecular bone in the mid-femoral neck (Paper III)

This study presents longitudinal changes in cortical thickness, cortical vBMD, trabecular vBMD as well as integral vBMD in specific regions of the mid-femoral neck in 400 older individuals (100 men and 300 women, aged 66-90 years). Segmental QCT analysis was used to estimate bone measurements in two anatomic sub-regions, the supero-lateral and infero-medial. At baseline women had lower bone parameters in the superior region than men. At follow-up all bone parameters were lower in women, except cortical BMD inferiorly. The relative losses in all bone parameters estimated in the superior region were substantial (about threefold) and significantly greater compared to those estimated in the inferior region that is mechanically loaded by walking (Voo et al. 2004). Women lost cortical thickness, integral vBMD and cortical vBMD more rapidly than men in both regions. The loss in trabecular vBMD was similar in both sexes and declined only in the superior region. As a result of these changes, the difference between men and women increased during the follow-up. Given the higher baseline values in men, the absolute decline in bone parameters were greater in women than men. Noteworthy also was that these differences between men and women were only weakly reflected in total femoral neck DXA-like results. Since fractures may initiate superiorly (de Bakker et al. 2009), the increased rate of superior femoral neck bone loss in women may contribute materially to the greater risk of femoral neck fracture in elderly women than men. Our results support the notion that endocortical resorption and possibly enlargement of intracortical cavities leading to trabecularization of the cortex may be key processes leading to increased bone fragility in the elderly femoral neck. Because of the marked difference in regional bone loss between individuals (see Fig 7.1) and also between the two sexes, better understanding of the so far undetermined mechanisms regulating localized bone loss in the elderly proximal femur is an important topic for future research.

Research Highlight

- The relative losses in all bone variables estimated in the supero-lateral mid-neck were substantially and significantly greater compared to those estimated in the infero-medial in both sexes.

- Women lost cortical thickness and cortical vBMD more rapidly than men in both regions; and this was only weakly reflected in total femoral neck DXA-like results.

- Women's higher rate of bone loss at critical locations may contribute materially to the greater risk of femoral neck fracture experienced by women than men.

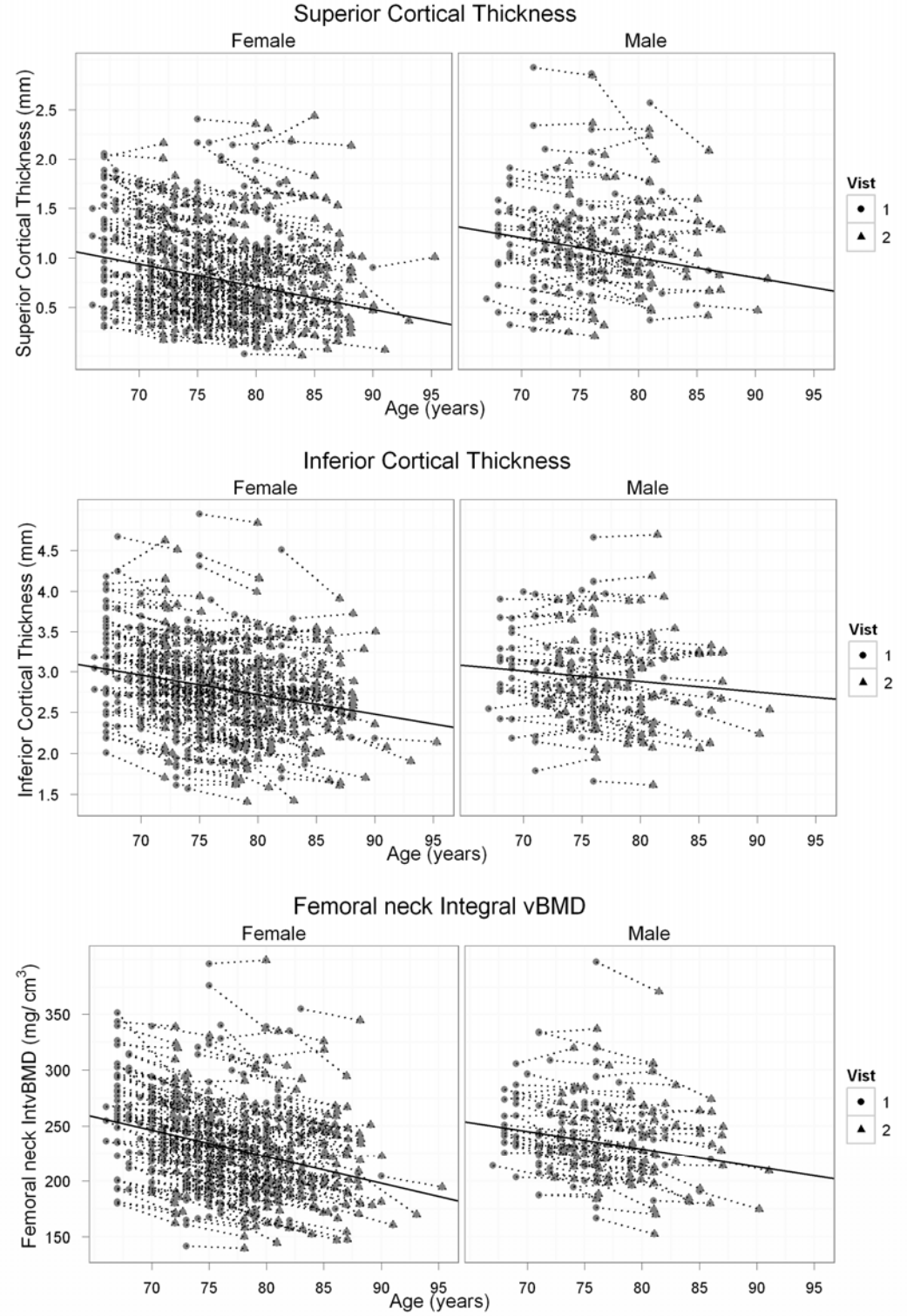

Figure 7.1: Individual change in estimated cortical thickness in superior and inferior surfaces and mid femoral neck vBMD in men and women during a median of 5.1 yr of follow-up. Each dot line represents a single participant. The solid line represents the average loss.

8 Discussion and future works

8.1 Discussion

We wondered if thinning of the cortex could be a good imaging biomarker for hip fracture for several reasons. Marked thinning of the superior cortex at the mid-femoral neck with advancing age has been described in cross-sectional studies (Boyce and Bloebaum 1993; Crabtree et al. 2000; Mayhew et al. 2005; Poole et al. 2010). Maximal compressive strain from a sideways fall on to the greater trochanter occurs in the superior femoral neck (Lotz et al. 1995; Pinilla et al. 1996; Carpenter et al. 2005; Mayhew et al. 2005; Verhulp et al. 2008) with maximal tensile strain in the inferior cortex (Thomas et al. 2009). It has been suggested that when falling onto the greater trochanter the crack that initiates an intracapsular fracture often initiates in the supero-lateral cortex (Carpenter et al. 2005; Mayhew et al. 2005; de Bakker et al. 2009; Thomas et al. 2009).

We have applied a segmental QCT analysis of the mid femoral neck to explore the utility of cortical thickness in four different regions for predicting incident femoral neck and trochanteric fracture in elderly men and women. Our results support our hypothesis that cortical thinning in the superior surface of the mid-femoral neck might be important in determining resistance to femoral neck fracture. In Cox proportional hazard models we found a greater risk of fracture with thinner superior cortices, although the effect was greatest in the SA quadrant. Furthermore, in both sexes SA Est CTh continued to make an independent contribution after adjustment for total femoral neck aBMD for FN fracture, whereas in men, SA and IP Est CTh were significant after adjustment for total femoral neck aBMD for TR fracture.

In our cross-sectional study the main contrast between fracture cases and controls was in the superior quadrants. Generally in our study the trochanteric fracture cases were thinner in the inferior neck compared to FN cases. In the TR fracture group the total femoral neck aBMD continued to make an independent contribution when combined with CTh. This is in agreement with Duboeuf et al. (Duboeuf et al. 1997) who found that upper femoral neck aBMD measurement is a better predictor of FN fracture than other areas of the hip. They concluded that hip BMD seems to play a more important role in the trochanteric than in the FN hip fracture.

The results from the longitudinal study showed that the losses in all bone variables estimated in the supero-lateral mid-neck were in relative terms substantial and significantly greater in comparison with those estimated in the infero-medial neck that is mechanically loaded by walking (Voo et al. 2004). In addition, the correlations between losses in the superior and inferior regions for each variable were only moderate or low. This low association between the losses in superior and inferior region requires explanation and may indicate different determining factors. The results of our cross-sectional study suggested that losses in cortical thickness with age differ considerably in men and women and are

markedly different according to location within the femoral neck. The longitudinal follow-up study verified all these findings and in addition we have shown that cortical thickness decreases with advancing age in men.

The longitudinal changes in cortical vBMD, trabecular vBMD and integral vBMD were also estimated. Women did not just lose more cortical thickness than men but also lost integral vBMD and cortical vBMD more rapidly than men in both regions. The loss in trabecular vBMD was similar in each sex and declined only in the superior region. As a result of these changes, the differences between men and women increased during the follow-up. At baseline, women had lower bone values in the superior region than men but at follow-up women were lower in all bone variables except for cortical vBMD specifically in the inferior region. In the cross-sectional study female controls had thinner CTh than male controls although in the infero-anterior quadrant (which is highly loaded during walking contrasting with the other quadrants) there was no difference in Est CTh. Interestingly, there were no difference in CTh between male and female femoral neck fracture cases. Both, percent differences in mean and cumulative distribution of femoral neck aBMD and SA Est CTh imply that the discrimination between FN cases and controls is sharper with cortical thickness. Noteworthy also was that these differences between men and women were only weakly reflected in total femoral neck DXA-like results. Therefore higher rates of bone loss at critical locations combined with increasing sex difference with advancing age may contribute materially to the greater risk of femoral neck fracture in elderly women. Our study suggests that, majority of elderly women and a minority of men have a substantially thinned cortex in the superior neck and therefore preventing falls in this population is of great importance in addition to strengthening the cortex if possible.

Our results have relevance for prevention of femoral neck fracture and for developing better explanatory mechanisms for this common fracture. The mechanical behaviour of a whole bone depends on the morphology of the bone as well as the intrinsic properties of the bone material itself. Therefore loss of cortical and trabecular bone must reduce the resistance to fracture in a fall. Cortical thinning in the superior surface of the mid-femoral neck has been shown to be important in determining resistance to femoral neck fracture in vivo (Johannesdottir et al. 2011; Poole et al. 2012) and maximal compressive strains from a sideways fall on to the greater trochanter occur there (Lotz et al. 1995; Pinilla et al. 1996; Carpenter et al. 2005; Mayhew et al. 2005; Verhulp et al. 2008). In an ex-vivo study the superior region of the mid-neck displayed marked trabecular micro-architectural weakness in elderly female femoral neck fracture cases (Milovanovic et al. 2012). It has been argued that the importance of trabecular bone for fracture resistance is increased if the femoral neck cortex fails through local buckling rather than through materials failure in which the superior cortex is crushed (Thomas et al. 2009). The study showed that, in both sexes, Est CTh declines in both superior and inferior surface but the relative loss was threefold greater superiorly whereas trabecular vBMD only declined in the superior region.

In a cross-sectional design it was explored if the association between muscular and bone parameters in the mid-thigh differs by age and sex in older people and additionally studied if those parameters were associated with incident low-trauma fractures in the lower limbs. There is discordance in the literature regarding the relationship between muscle and bone in older adults. In the present study, muscular area and knee extensor strength were positively associated with total shaft area and cortical area, similarly in both sexes.

However the muscular parameters explained less than 10 % of the variability in total shaft and cortical area when corrected for age, height, and weight.

Among the measured bone variables, the size of the medullary area and the consequent thinning of the cortex with higher buckling ratio were significantly associated with lower limb fractures in both sexes. The bone parameters most strongly associated with fractures were, however, mostly independent of baseline muscular parameters. Increasing thigh muscle strength was, however, a significant independent protective factor against fractures in a multivariable hazards model. These factors were independent of the bone variables, which could suggest that muscle mass and strength might act by preventing falls rather than acting directly on bones.

Variations in muscular parameters with age were parallel in both sexes but the measured bone parameters varied differently with age by gender, considerably more so in women than men. The variations with age in cortical thickness were threefold greater in women than men, almost fourfold greater for MA and BR, with no difference in total shaft area. These variations with age reflect presumably greater endocortical resorption but minimal periosteal apposition.

These three studies are in agreement with findings suggesting that endosteal resorption is responsible for the cortical thinning associated with aging in the femoral neck and shaft and associated with lower limb fracture, especially femoral neck fracture, that is not fully compensated by periosteal apposition in either sex. The results support the notion that endocortical resorption and possibly enlargement of intracortical cavities leading to trabecularization of the cortex may be key processes leading to increased bone fragility in the elderly femoral neck and in the lower limbs. These findings also raise the question of whether a practical intervention could be found that would strengthen the superior femoral neck. Because of the marked difference in regional femoral neck bone loss between individuals and also between the two sexes, better understanding of the so far undetermined mechanisms regulating localized bone loss in the elderly proximal femur is an important topic for future research.

8.2 Strength and limitation

These study series have several important strengths such as the inclusion of both men and women and the spatial resolution QCT-scans were made and analyzed at a single-center. All measurements were performed on data acquired before the occurrence of fractures, and cases and controls are part of the same cohort, which ensure their comparability. In two of the studies we used our detailed information on medication allows exclusion of persons on medications that may influence bone metabolism.

These study series also have some limitations. All of our subjects were Caucasian, and our results may therefore not be applicable to other ethnic groups. In the cross-sectional study of the femoral neck we evaluated a limited number of QCT structural parameters because of the adverse trade off between multiple testing and the limited number of cases for inclusion at this stage in the AGES study. No trochanteric measurements were included in part because we had no way of validating their accuracy as was done in previous work for the femoral neck by Mayhew et al. (Mayhew et al. 2005). So we cannot exclude that

assessment of both femoral neck and trochanteric measurements might give different results. There are certain technical limitations in the measurement of regional cortical thickness in vivo. What we have measured with the BIT2 technique cannot be considered an accurate estimate of the thickness of the cortex in the thin superior zones, especially when CTh was estimated in quadrants, due to the partial volume effect and the tendency to underestimate the thin cortices to zero. For simplicity in application, we used a single threshold to delineate cortex from trabecular bone. The difficulties of resolving thin bone cortices in the femur using a thresholding technique were documented recently (Treece et al. 2010). 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 (Prevrhal et al. 2003; Davis et al. 2007). These effects lead to cortical thickness overestimation particularly in the inferior region of the femoral neck cortex. Downward bias can also occur when true cortical thickness approaches the pixel size, especially for highly porous cortices (Davis et al. 2007) and this might affect our results more in women than men because of thinner cortexes among women. Higher apparent cortical density in the inferior regions compared to the superior regions appeared exaggerated compared to direct measurements made with a scanning electron microscope (SEM) technique (Loveridge et al. 2004). Nevertheless, by average adjacent CTh measurements both in cross-sectional parts and along the femoral neck axis increase the precision, the CVs are comparable to those obtained in 2D Hip Strength Analysis (Khoo et al. 2005) and to CVs of the architectural parameters estimated by HR-pQCT (Walker et al. 2009; Wang et al. 2009) while remaining larger than CVs for 2D BMD (Lorentzon et al. 2006). As discussed by Kaptoge et al.(Kaptoge et al. 2008), 2-D BMD's generally excellent coefficients of variation give it an advantage for diagnostic purposes over less precise outcome measures, even though it may be less directly related to the predisposing cause of hip fracture. While partial volume errors clearly affect true estimates, they are unlikely to mask large trends.

In the mid-thigh study the cross-sectional nature of the data may underestimate the true rate of decline/increase with age as shown by some longitudinal studies (Lauretani et al. 2008; Riggs et al. 2008). Thus, our findings could have been affected by secular changes in muscle mass or bone mass that occurred over the age span of our cohort or by a confounding effect of fat (Reid 2008). Isometric knee extensor strength and body weight are only surrogate estimates of the strains applied on the mid-thigh. We did not have an estimate of BMD or porosity in the femoral shaft cortex; previous studies of older individuals have reported no effect of exercise on cortical volumetric BMD (Daly and Bass 2006; Bailey et al. 2010). Finally, it is a limitation that there were no measurements of sex hormones in the participants.

8.3 Future works

The study series of this dissertation suggest that because of the marked difference in regional bone loss between individuals and also between the two sexes, better understanding of the so far undetermined mechanisms regulating localized bone loss in the elderly proximal end of femur is an important topic for future research. Especially because BMD and CTh are strongly associated with fracture risk in both men and women (Cummings et al. 1993; Black et al. 2008; Johannesdottir et al. 2011). In addition, since the decrements inferiorly and superiorly seem to be only moderately to weakly associated the

possibility exists that there could be different mechanisms for bone loss at each site, which might have consequences for prevention. One of the near-future goals are to study the association between age-related bone loss at the femoral neck (in cortical BMD, trabecular BMD and CTh) and nutritional and lifestyle factors as well as osteoporotic drugs use (bisphosphonate and hormone replacement therapy). The nutritional and lifestyle factors would include physical activity, muscular strength, smoking, vitamin-D in diet, serum 25OHD, parathyroid hormone (PTH) and sex hormones especially estradiol level. The findings from these study series also raise the question of whether a practical intervention could be found that would strengthen the superior femoral neck.

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