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RADIOGRAPHICAL
ASSESSMENT OF
HIP FRAGILITY

FACULTY OF MEDICINE,
INSTITUTE OF BIOMEDICINE,
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**RADIOGRAPHICAL ASSESSMENT OF
HIP FRAGILITY**

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Abstract

The current benchmark for the assessment of fracture risk is the status of osteoporosis based on the measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). However, DXA-based BMD has been shown to lack predictive ability for individual fracture risk. More than half of the hip fractures occur among people who are not classified as having osteoporosis. Osteoporosis (i.e. reduced bone mass) is only one risk factor for a fracture. In addition to bone mass, the mechanical strength of a bone is influenced by material and structural factors. However, we have limited information about the combined effects of BMD and bone structural properties in the evaluation of fracture risk, with regard to different types of hip fractures in particular. Therefore, this study investigated the radiograph-based structural factors of the upper femur for the assessment of bone mechanical competence and cervical and trochanteric hip fracture risk.

The subjects of the clinical study comprised 74 postmenopausal women with non-pathologic cervical or trochanteric hip fracture and 40 age-matched controls. The impact of bone structure on the bone mechanical competence was studied using the experimental material of 140 cadaver femurs. The femora were mechanically tested in order to determine the failure load in a side impact configuration, simulating a sideways fall. In all study series, standard BMD measurements were performed, and the structural parameters of bone were determined from digitized plain radiographs.

The present study showed that the large variation in the mechanical competence of bone is associated with the geometrical and architectural variation of bone. Moreover, the results strongly suggested that the etiopathology of different types of hip fractures significantly differs, and that fracture risk prediction should thus be performed separately for the cervical and trochanteric hip fractures. Furthermore, the study implied that the current clinical procedure can better be used for the assessment of the risk of trochanteric fracture, whereas cervical fracture is more strongly affected by the geometrical factors than by BMD. Finally, radiograph-based structural parameters of trabecular bone and bone geometry predicted *in vitro* failure loads of the proximal femur with a similar accuracy as DXA, when appropriate image analysis technology was used. Thus, the technology may be suitable for further development and application in clinical fracture risk assessment.

Keywords: biomechanics, bone mineral density, bone structure, cervical fracture, DXA, fracture risk, hip fracture, osteoporosis, radiography, trochanteric fracture

To my family

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Abbreviations

ANCOVA	Analysis of covariance
AO	Arbeitsgemeinschaft für Osteosynthesefragen
AW	Acetabular width
BMD	Bone mineral density
BMI	Body mass index
CFC	Medial calcar femoral cortical thickness
CI	Confidence interval
DXA	Dual-energy X-ray absorptiometry
EN	Euler number
FEBMD	Femoral neck bone mineral density
FNAL	Femoral neck axis length
FNC	Femoral neck cortex thickness
FRAX TM	WHO Fracture Risk Assessment Tool
FSC	Femoral shaft cortex thickness
FSD	Femoral shaft diameter
GLCM	Gray-level co-occurrence matrix
HAL	Hip axis length
HD	Femoral head diameter
HI	Homogeneity index
HSA	Hip structural analysis
MRI	Magnetic resonance imaging
ND	Femoral neck diameter
NHANES	National Health and Nutrition Examination Survey
NSA	Femoral neck-shaft angle
OP	Osteoporosis
OR	Odds ratio
pQCT	Peripheral quantitative computed tomography
QCT	Quantitative computed tomography
QUS	Quantitative ultrasound
RMS CV	Root-mean-square average of coefficient of variation
ROC	Receiver operating characteristic curve
ROI	Region of interest
RR	Risk ratio
TBA	Trabecular bone area
TMO	Trabecular main orientation

TRBMD	Trochanteric bone mineral density
TW	Trochanteric width
WABMD	Ward's triangle bone mineral density
WHO	World Health Organization

List of original publications

This thesis is based on the following articles that are referred to in the text by their Roman numerals:

- I Pulkkinen P, Partanen J, Jalovaara P & Jämsä T (2004) Combination of bone mineral density and upper femur geometry improves the prediction of hip fracture. *Osteoporos Int* 4: 274–280.
- II Pulkkinen P, Partanen J, Jalovaara P & Jämsä T (2008) In contrast to bone density, bone geometry can discriminate cervical hip fractures in non-osteoporotic females. Manuscript.
- III Pulkkinen P, Eckstein F, Lochmüller E-M, Kuhn V & Jämsä T (2006) Association of geometric factors and fracture load level with the occurrence of cervical vs. trochanteric hip fractures. *J Bone Miner Res* 21: 895–901.
- IV Pulkkinen P, Eckstein F, Lochmüller E-M, Kuhn V, Nieminen MT & Jämsä T (2008) Experimental hip fracture load can be predicted from plain radiography by combined analysis of trabecular bone structure and bone geometry. *Osteoporos Int* 19: 547–558.

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1 Introduction

Hip fractures have been considered to be the most serious outcome of osteoporosis (Cummings & Melton 2002), and they are the most common reason for acute orthopaedic admission in older people (Parker & Johansen 2006). The current benchmark for the assessment of fracture risk is the status of osteoporosis based on the measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). However, DXA-based BMD has been shown to lack in the predictive ability for the individual fracture risk (Wilkin & Devendra 2001, Kanis 2002, Stone *et al.* 2003, Schuit *et al.* 2004). The majority of hip fractures occur among people who can not be classified as having osteoporosis using the DXA-based BMD T-score threshold value of -2.5 (Stone *et al.* 2003, Schuit *et al.* 2004). Thus, it is important to find new strategies for identifying the individuals under high risk of hip fracture, and with a need of treatment. Indeed, substantial efforts have recently been put in studies to elucidate the causal relationships between different risk factors of hip fractures.

The limited ability of BMD to predict fracture is not surprising as the etiology of fracture is multifactorial (Kanis 2002, Fyhrie 2005, Järvinen *et al.* 2005, Sambrook & Cooper 2006, Sievänen *et al.* 2007a, Cheung & Detsky 2008, Järvinen *et al.* 2008). Reduced bone mass is only one risk factor for a fracture. In addition to bone mass, several other aspects have an effect on bone mechanical competence and consequently on fracture risk. It is generally accepted that the mechanical strength of a bone is influenced by material and structural factors. Bone strength is thus attributable to the interaction of material properties, the amount of material as well as morphological and architectural properties (i.e. the trabecular structure). (Järvinen *et al.* 2005, van der Meulen *et al.* 2001, Ammann & Rizzoli 2003, Hernandez & Keaveny 2006)

Today we have indisputable evidence that the measurement of BMD is not sufficient for a relevant prognosis of individual fracture risk (Wilkin & Devendra 2001, Kanis 2002, Stone *et al.* 2003, Schuit *et al.* 2004, Cheung & Detsky 2008), and that the assessment of bone structure is also important (Järvinen *et al.* 2005, Ammann & Rizzoli 2003, Alonso *et al.* 2000, Legrand *et al.* 2000, Benhamou *et al.* 2001, Partanen *et al.* 2001, Gnudi *et al.* 2002, Chappard *et al.* 2005, El-Kaissi *et al.* 2005). However, we have limited information about the combined effects of BMD and bone structural properties for the assessment of the mechanical competence of bone and the evaluation of fracture risk, in particular in different types of hip fractures.

This study therefore focused on combining the different structural impacts of the upper femur for the assessment of hip fragility. The behaviour of different hip fracture types was elucidated separately in order to test the hypothesis that cervical and trochanteric hip fractures have different explanatory factors. Radiography, the widely available imaging modality, which also has a potential for screening purposes (Lespessailles *et al.* 2006), was used to test whether it is applicable for the evaluation of bone mechanical competence and consequently for fracture risk assessment.

2 Review of literature

The existence of humans would be at least impractical and inert without the skeleton that is composed of a well-organized structure of more than 200 bones. The bones provide mechanical support for the human body. In addition to this role of mechanical support structure, bones also have a lot of other vital functions. Bones serve as a protection for internal organs, as a mineral reservoir in mineral homeostasis, and also as a primary site for the formation of blood cells. In general, the mass, size and shape of bone are optimal for the structural strength and functions of bone (Seeman & Delmas 2006).

In the following literature review, a basic overview of the structure and physiology of the healthy bone as well as of the factors affecting the mechanical competence of bone will be presented briefly. At the end of the literature review, the focus will be narrowed down to the topic of this thesis; the etiopathology of hip fractures and the assessment of hip fracture risk.

2.1 Overview of the structure and physiology of the bone

Bones compose the human's skeleton, which is basically a dynamical locomotive apparatus. For the optimal operation of this function, bones can continually adapt to habitual loadings (Wolff 1892, Frost 1994, Frost 2003). Consequently, bone can be characterized as a dynamical tissue having active physiological operations to compose and maintain the structure in an appropriate manner. A brief description of the structure and physiology of bone will be given next.

2.1.1 Bone structure

Bone material

Bone is a composite material including bone cells and extracellular matrix and it has inorganic and organic components. 70% of bone weight is inorganic mineral matter, of which 95% consists of hydroxyapatite crystals $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$. The remaining 30% consists of water and an organic component of extracellular matrix made up mainly of type I collagen proteins and bone specific cells, i.e. osteoblasts, osteoclasts, and osteocytes. (Jee 2001, Ganong 2005)

Structural design of bone

Different material distribution constitutes different structures. The material distribution also differs significantly between bones with different shapes, e.g. between flat bones as in the skull, and long bones as in the limbs.

In long bones, the external shape can be characterized by an expansion at both ends (epiphysis), a hollow cylindrical tube in the middle (diaphysis), and the area between these parts (metaphysis). The material distribution also differs inside the bone. Morphologically, there are two different bone types in the skeleton, i.e. the bones are composed of two different types of bone tissue. Characteristics of these bone types in the skeleton are presented in Table 1.

The cortical bone that makes up the outer layer of bone is compact and dense, while the trabecular bone that is located in the interior of flat bones and at the epiphyseal and metaphyseal areas of long bones is the spongy, porous type of bone. Both bone types are composed of the same cells and the same matrix elements, but differ in structural and functional properties. The trabecular bone is composed of interconnected bone rods and plates called trabeculae, which construct the bone network. While the compact cortical bone borders the structure, it can be considered to define the external shape of bone at the macroscopic level, whereas the trabecular bone network defines the inner architecture of bone.

From the perspective of mechanical strength it may be postulated that the structure is the strongest if it is solely composed of cortical bone. However, the skeleton is basically the locomotive apparatus. Consequently, too massive and solid structure is not practical. It has been suggested as early as 1892 by Wolff that bone mass is optimal in relation to the mechanical strength of bone (Wolff 1892). Wolff has postulated that “every change in the form and function of bone, or of their function alone, is followed by certain definite changes in their internal architecture, and equally definite alteration in their external conformation, in accordance with mathematical laws” (Wolff 1892, Frost 1994).

The cortical bone, which forms approximately 80% of the skeleton, has a structural, load-bearing function, and it is mainly responsible for the bending resistance of the bone (Seeman & Delmas 2006, Jee 2001, Augat & Schorlemmer 2006, Seeman 2008). Even if the trabecular bone is a minority of the total bone mass in the skeleton, it can be characterized by a high surface-to-volume ratio (Table 1). Owing to this the trabecular bone is mainly responsible for bone metabolism (Ganong 2005). Consequently, the changes in the bone structure can be seen more quickly in the trabecular than in the cortical bone (Silva & Gibson

1997, Eriksen *et al.* 1990). In addition, the trabecular bone contributes to the mechanical strength, as well (Felsenberg & Boonen 2005). This will be discussed in more detail in the context of bone mechanical competence.

Table 1. Characteristics of cortical and trabecular bone in the skeleton. (Adopted from Jee 2001).

	Cortical bone	Trabecular bone
Skeletal mass (%)	80	20
Bone surface (%)	33	67
Surface/volume (mm ² /mm ³)	2.5	20
Fractional volume (mm ³ /mm ³)	0.95	0.20

2.1.2 Bone physiology

Bone and lifespan

The quantity, quality and shape of bone continuously change during the lifetime to maintain skeletal integrity. Bone mass increases during youth. It reaches the peak mass approximately at the age of 25–30 years. After the age of 30–35 the amount of bone will start to decrease. In females, there is an accelerated loss of bone after menopause. They will lose about half of their peak bone mass by the age of 80, while the same proportion is 25–30% in males (Väänänen 1996).

Bone turnover process – modelling and remodelling

Bone can be characterized as a dynamical tissue, which can, and which has to adapt to continuously variable loading conditions in order to maintain the skeletal integrity. The mechanisms responsible for the adaptive turnover process of bone are modelling and remodelling.

Bone modelling takes place mainly during growth, but also in conditions of altered mechanical loading, where simultaneous bone resorption and formation are produced at different sites (Frost 1987, Seeman 2003b). Bone remodelling is defined as the resorption of bone followed by bone formation in the same region. This is an adaptive process, where the bone responds to changes in loading conditions and replaces old bone or weakened structures with a new tissue. (Seeman 2003b) In general, there is a coupling between the formation and resorption of bone. Consequently, the same amount of bone is resorbed and

formed. Later in life, bone resorption begins to dominate over formation, causing bone loss.

The regulation of bone turnover

There are specific cells in bone that are responsible for the modelling and remodelling processes. Bone matrix is produced and mineralized by the bone productive cells, osteoblasts, whereas bone resorption is caused by the bone-resorbing cells that are called osteoclasts. After the bone is mineralised by the osteoblasts, some of them will have surrounded themselves with mineralized bone tissue, and are called as osteocytes, the mature bone cells.

For normal skeletal maintenance, over 20% of bone mass is remodelled in a year. The remodelling is also needed in the repairing of damages in the bone. It is estimated that about 20% of the trabecular bone and 4% of the cortical bone is annually renewed in mature people (Ganong 2005).

The mechanism for the execution of bone formation and/or resorption in an appropriate site is very complicated and partly unknown, but some theories have been suggested. The theory presented by Frost suggests that the regulation is under the mechanobiological feedback mechanism called “Mechanostat” (Frost 1987, Frost 2003). According to this theory, mechanostat adjusts bone formation and/or resorption according to the local stresses and strains caused by mechanical stimuli. In other words, bone is formed in areas subjected to high stress by activating osteoblasts there, whereas it is resorbed in areas under a slight stress by the osteoclasts activation.

The theory has encountered criticism as it oversimplifies the process and can not explain all the bone adaptation phenomena (Turner 1999, Skerry 2006). Some cellular and neural mechanisms are also needed for the activation and/or deactivation of bone cells, but other factors, such as those associated with calcium regulation, also contribute to the process. These factors, however, are not discussed here, since “an attempt to predict the structural functions of the bones from its cell- and molecular-biologic features would be analogous to predicting macrocosms from microcosms”, as Järvinen *et al.* (2005) cite Frost and Jee (2003).

2.2 Bone mechanical competence

In general, bone mechanical competence can be condensed as the bone's ability to resist fracture. One central factor for the susceptibility of fracture is naturally bone mechanical strength. It has been generally accepted that the mechanical strength of bone is influenced by the material and structural factors, i.e. bone strength is attributable to the interaction of material properties, the amount of material, morphology and architectural properties (i.e. the trabecular structure) (Järvinen *et al.* 2005, van der Meulen *et al.* 2001, Hernandez & Keaveny 2006).

On the other hand, the term “bone quality” has been defined by a National Institutes of Health conference as “the sum total of characteristics of the bone that influence the bone's resistance to fracture” (Fyhrie 2005). This widely used term has been launched to represent factors that affect bone mechanical competence, but it is however somewhat imprecise and confusing and has thus encountered criticism (Sievänen *et al.* 2007a, Cheung & Detsky 2008). Anyway, it is clear that if bone quality is important in determining fracture risk, it must play a role in determining bone mechanical properties (Järvinen *et al.* 2005, Hernandez & Keaveny 2006).

Despite the confusing terminology in the literature, there is a consensus that the red thread for the definition of bone mechanical competence or bone quality is, in the end, the probability of fracture occurrence. Thus, it is easy to understand that there are a lot of different factors that have an effect on it. Basically, the extra-skeletal risk factors that affect the risk of fracture can be excluded from the term and they will be discussed later in the context of fracture risk.

2.2.1 Factors attributable to bone mechanical competence

Järvinen *et al.* (2005) have presented a schematic illustration of the central components that have an influence on the bone mechanical competence (Fig. 1). The material properties are defined by the tissue-level quality of the bone material, while the structural properties characterize the bone as a whole anatomic unit. Summary for some physical characteristics of bone that may influence biomechanical competence of bone is shown in Table 2, categorized by physical scale. The effects of these factors for bone mechanical competence are overviewed next.

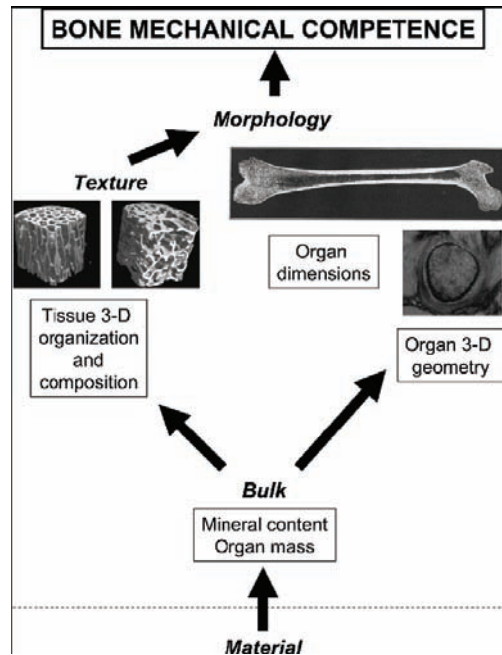


Fig. 1. A schematic illustration of the components of the mechanical competence of whole bones according to Järvinen *et al.* (2005). The material properties are defined by the tissue-level quality of the bone material, while the structural properties characterize the bone as a whole anatomic unit. (Reproduced from *J Bone Miner Res* 2005; 20: 717–720 with permission of the American Society for Bone and Mineral Research).

Bone material properties

Bone material properties are mainly determined by the calcification of bone matrix and microstructural factors such as the composition and spatial arrangement of collagen fibers and crystals (Table 2). The most important material property of bone is the degree of the mineralization of its tissue. (Seeman 2003a)

Table 2. Summary for some physical characteristics of bone that may influence biomechanical competence of bone, categorized by physical scale. Modified from Hernandez & Keaveny (2006).

Scale (m)	Bone characteristics
$> 10^{-3}$	Whole bone morphology (size and shape) Bone density spatial distribution
10^{-6} – 10^{-3}	Microarchitecture (trabecular bone architecture) Porosity Cortical shell thickness
10^{-9} – 10^{-6}	Mineral and collagen distribution/alignment Microdamages (type, amount, distribution)
$< 10^{-9}$	Collagen structure and cross-linking Mineral type and crystal alignment Collagen-mineral interface

Material stiffness is mainly defined by the inorganic mineral component while the organic component is responsible for material elasticity. The mineral constituent resists compression forces very effectively, whereas the tensile strength of bone is more regulated by collagen. The balance between the material properties of bone and the bone's flexibility is achieved by varying its mineral content. (Seeman & Delmas 2006) When the mineral content increases the material stiffness also increases, whereas the flexibility decreases. In undermineralized state the bone becomes too flexible and is exposed to fracture. On the other hand if the bone is overmineralized, it will become brittle, which also increases its susceptibility to fracture. (Seeman 2003a)

The material properties of bone are quite similar among all mammals. The age-dependent changes in the material properties, as well as material differences between genders or species, are less important for the mechanical integrity of the bone when compared to bone mass and architecture. (Frost 1997, Currey 2001)

Bone structural properties – geometry and architecture

Bone structural properties include features such as bone size and bone macroscopic geometry as well as microstructural properties such as trabecular bone architecture (Table 2). The structural properties of bone are determined by the combination of material and geometrical as well as architectural properties and are evident when the bone is considered as a whole functional unit. (Currey 2001, Currey 2003) Different bones are constructed differently in different

skeletal sites, depending on their usual functions. However, the construction principle remains the same in all cases; to achieve lightness and to minimize the amount of material needed to achieve the appropriate bone strength (Seeman 2008). This is further achieved by the architectural design of the bone, i.e. by fashioning the mineralized bone tissue in an appropriate manner.

Bone geometry can be thought to define the macroscopic shape of bone, whereas bone inner architecture can be understood as the structure of the trabecular bone, which itself as the number and orientation of the trabeculae, the thickness of trabecular plates and/or rods as well as the connections of the trabeculae. From a mechanical point of view the trabeculae are arranged to provide the greatest strength with the minimum of material in positions of maximum stress. (Currey 2003, Keaveny *et al.* 2001)

The trabecular bone inside the long bone ends mainly carries the axial compressive forces, whereas the macroscopic bone geometry (bone physical size, cortical thickness, etc.) is responsible for bone stiffness, i.e. for the resistance to bending and torsional forces. The role of the compact bone tissue in the long bones is to build up lever that can resist deformation, whereas the trabecular bone in the vertebrae and in the end of long bones can be compared to a spring, since it has a good ability to absorb energy without breaking, i.e. it can change shape and restore again without changes in the original structure. (Seeman 2008) Tubular bones can deform by only 1–2% of their original length, whereas vertebral bodies can deform to a greater degree because of their ability to absorb energy (Seeman 2008).

It is well documented that bone geometry plays an important role in the mechanical strength of the bone, and thus also in the fracture risk (Augat *et al.* 1996, Lang *et al.* 1997, Crabtree *et al.* 2001, Gnudi *et al.* 2002, Lochmüller *et al.* 2002, Augat & Schorlemmer 2006). Geometrical measures, including bone size, predict up to 70–80% of whole bone strength (Augat & Schorlemmer 2006). However, the role of the cortical bone may not be so prominent at skeletal sites where the cortical shell is particularly thin and the proportion of the trabecular bone is high, such as in the vertebrae, where the proportion of the trabecular bone is as high as 66% to 90% (Einhorn 1992). The support of the internal trabecular structure is essential at these skeletal sites (Järvinen *et al.* 2005).

Even though the superiority of cortical bone to trabecular bone in terms of whole bone strength has been established in several studies, (Augat *et al.* 1996, Bell *et al.* 1999, Crabtree *et al.* 2001) changes in bone microstructure, loss of connectivity and removal of trabeculae can also significantly decrease bone

strength (Eriksen *et al.* 1990, Silva & Gibson 1997, Legrand *et al.* 2000, Benhamou *et al.* 2001, Chappard *et al.* 2005, Felsenberg & Boonen 2005, Hudelmaier *et al.* 2005, Hernandez & Keaveny 2006).

2.2.2 Age-related changes in bone structure and bone mechanical competence

Since bone is a dynamical tissue, changes happen continuously both in the bone geometry and architecture during life. The bone structure does not only change during growth and maturation but also in ageing. All these structural changes may be crucial for the bone strength. In general, changes in the mechanical competence of bone are explained by the functional adaptation of the bone structure and the age-related deterioration of bone mechanical properties. (Augat & Schorlemmer 2006)

Long bones grow in length and diameter and bone mass increases in proportion to the enlarging volume of the whole bone in childhood and adolescence. A bone with a large mass and cross-sectional area is more resistant to compressive forces than a bone with the opposite properties simply because the load is distributed over a larger surface area. In contrast, the dimensions of a bone are more important than its mass or density when the bone is subjected to bending or torsional forces. Here the bone mass should ideally be distributed as far away from the neutral axis of the load as possible for maximal strength. (Keaveny *et al.* 2001) From this perspective, endosteal resorption and periosteal formation change the cortical bone geometry and the spatial apposition of bone mass during growth. During puberty, males have a high rate of periosteal apposition leading to cortical thickening and wider bones. In females, periosteal formation is inhibited and endocortical formation is stimulated leading to cortical thickening and the narrowing of the medullary cavity. During ageing periosteal apposition continues causing the redistribution of bone tissue away from the long axis of bone which allows the bone to resist bending and torsional loads better. (Seeman 2001)

Similar positive changes can also be seen in the trabecular bone. Vertebral bodies increase in length, width, and depth during growth. The length and thickness of trabecular plates increase in proportion to the enlarging vertebral body (Seeman 2003a), thus designing the bone to resist compressive forces.

However, the structure of bone diminishes in ageing. One indication is the loss of bone tissue that can change both the bone geometry and architecture, causing the weakening of bone mechanical competence. Bone loss produces

structural damages, such as cortical and trabecular thinning, intracortical porosity, complete loss of trabecular plates and loss of connectivity. (Seeman 2003a) The majority of the bone mass that is lost in postmenopausal women is from the deterioration of the trabecular bone (Silva & Gibson 1997). This is most likely the result of a more rapid rate of bone turnover in the trabecular bone compared with the cortical bone (Eriksen *et al.* 1990). Because the amount of trabecular bone in the vertebrae is high, this deterioration is particularly apparent in the spine and consequently predisposes to compression fracture of the vertebra (Felsenberg & Boonen 2005). On the other hand, the cortex thinning and the increasing porosity of cortical bone predispose to buckling, microdamage and finally to ultimate fracture in long bones, as well.

2.3 Evaluation of bone mechanical competence *in vitro* using biomechanical testing

When the bone is subjected to loading, the ability of the bone to carry loads depends on its mechanical properties. The mechanical properties of whole bone as well as machined bone samples can be evaluated using biomechanical testing, where a specimen is subjected to a compressive, tensile, torsion or bending force. Mechanical tests have typically been used not only to determine the mechanical strength of bone but also to estimate, which non-invasive methods are able to define bone mechanical competence (Genant *et al.* 1996, Cummings *et al.* 2002).

The numbers of different loading configurations have been constructed to obtain bone mechanical properties. However, not all of them are reviewed here. Since this thesis is focused on hip fractures, only tests typically used for the assessment of the proximal femur mechanical competence will be discussed.

2.3.1 Biomechanical testing of the proximal femur

The proximal femur is the subject of particular clinical interest, because the number of hip fractures has dramatically increased, and these fractures involve enormous socio-economic problems (Cooper *et al.* 1992, Ismail *et al.* 2002, Cummings & Melton 2002, Parker & Johansen 2006). Therefore, due to the high clinical relevance, there is a large scale of publications regarding the mechanical tests of the proximal femur. The tests have typically been performed using the axial loading of the femoral head (Leichter *et al.* 1982, Alho *et al.* 1988, Beck *et al.* 1990, Augat *et al.* 1996, Eckstein *et al.* 2002, Lochmüller *et al.* 2002,

Lochmüller *et al.* 2003) or a side-impact configuration (Fig. 2) (Courtney *et al.* 1994, Courtney *et al.* 1995, Pinilla *et al.* 1996, Cheng *et al.* 1997b, Eckstein *et al.* 2002, Lochmüller *et al.* 2002, Lochmüller *et al.* 2003, Eckstein *et al.* 2004).

To measure femoral neck strength using the axial loading configuration, the proximal end of the femur is mounted on a stage and load is applied to the femoral head until the femoral neck fractures (Fig. 2, left). The axial test is performed having the diaphyseal mid-axis either vertical as in the figure or rotated 10-15° to simulate single-leg stance (Shah *et al.* 1993, Lang *et al.* 1997, Keyak *et al.* 1998, Cody *et al.* 1999, Keyak *et al.* 2001). The side-impact configuration simulates fall on the greater trochanter and provides valuable information about the biomechanics of the human hip under realistic loading conditions (Fig. 2, right).

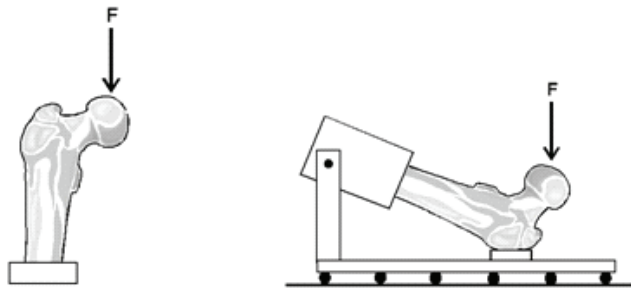


Fig. 2. Biomechanical testing of the proximal femur. To measure femoral neck strength in the axial direction (left), the proximal end of the femur is fixed on a loading stage by a supporter plate and force is applied directly to the upper side of femoral head until the femoral neck fractures. The side-impact configuration (right) simulates fall on the greater trochanter and provides valuable information about the biomechanics of the human hip under realistic loading conditions.

2.3.2 Mechanical properties of bone derived from mechanical testing

In the destructive bone biomechanical testing the test specimen is loaded until it fails. The load and the corresponding deformation of the specimen are recorded during loading and a load-deformation curve is drawn (Fig. 3). The mechanical properties of bone are derived from this plot. The elastic region is the linear part of the graph where all changes in the specimen are reversible. Therefore, some mechanical properties can also be tested non-destructively. The yield-point is the

transition point from the elastic region to the plastic region, where the first non-reversible changes appear in the sample.

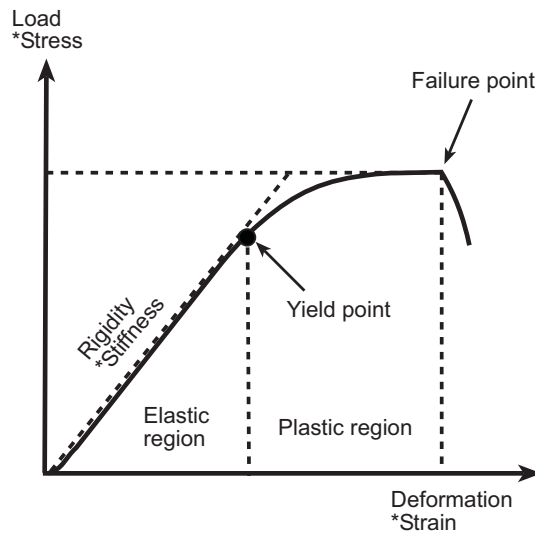


Fig. 3. Typical load-deformation curve resulting from a biomechanical test of a bone specimen. The mechanical characteristics presented in the figure can be described at the structural level of the whole anatomical unit (extrinsic properties) or at the tissue level of bone material (intrinsic properties, which are denoted with an asterisk in the figure). The extrinsic parameters can be recorded directly from the load-deformation curve, whereas the intrinsic parameters can be obtained from the stress-strain curve by converting the load to stress and deformation to strain. The elastic region is the linear part of the curve where all changes in the specimen are reversible. The yield point is the transition point from the elastic to the plastic region, where the first non-reversible changes appear in the sample. The slope of the linear part of the curve is rigidity (stiffness i.e. elastic modulus), and the area under the curve represents absorbed energy (toughness), i.e. the energy required to break the sample.

The mechanical characteristics of bone can be described at two levels. The extrinsic properties describe the bone at the structural level as a whole anatomical unit, whereas the intrinsic properties are defined by the tissue-level quality of the bone material. The extrinsic parameters can be recorded directly from the load-deformation curve. The intrinsic parameters on the other hand can be obtained from the stress-strain curve by converting the load to stress (force/unit area) and deformation to strain (proportional change in the length as percentage or microstrain).

There are a number of mechanical parameters available from the load-deformation graph (or stress-strain graph) that can be used to indicate bone fragility, such as bone stiffness, strength (load), toughness, post-yield deformation and fatigue properties. At present, it is not yet clear which of these assays are most closely related to the fracture incidence (Augat & Schorlemmer 2006, Hernandez & Keaveny 2006), although strength is the most intuitive, since it directly relates to the force capacity of bone for a single event (Hernandez & Keaveny 2006).

2.3.3 Factors affecting the interpretation of mechanical properties

Van der Meulen *et al.* (2001) have straightforwardly stated that “skeletal functional integrity can be assessed by structural strength tests that measure how well the whole bone can bear loads” and that “there is no alternative to testing whole bone strength and conclusions regarding bone mechanical function based solely on geometry or bone mineral content are inappropriate and likely misleading”.

Theoretically, this might be granted. However, even this might not be enough. John D. Currey has concisely stated that “there are innumerable influences on the strength that bone will actually show in life. In interpreting studies made in the laboratory we must remember, for instance, that static tests, though useful, are different from the situation in which bone usually breaks in life” (Currey 2002).

The entire bone has a very complex structure, having bone tissue with locally varying shape and architecture. Consequently, the absolute strength measurement of this complex unity, for example, is rather utopian. Strength, as such, should have a clear physical meaning; it can be associated with Newton, with the force that is needed for the breaking of bone, but not straightforwardly and exclusively with the risk of fracture. Cheung & Detsky (2008) have noted that bone strength is only one determinant of fracture risk and that the ability to avoid injury to the bones is another. Moreover, experimental tests can not elucidate for instance the bone’s ability to repair damages.

Even if the occurrence of fracture is the end point in real life, the biomechanical tests aimed to evaluate bone mechanical competence can, however, provide a useful tool for investigators. Naturally, the probability of fracture increases if the bone strength is reduced. What should, however, be clear is that realities observed in epidemiological studies can not be reformulated based on the experimental studies carried out in a laboratory.

In addition to the previous “philosophical” viewpoint, there are also important physical factors to be taken into account in the interpretation of results obtained in experimental studies. From the perspective of biomechanics, bone is an anisotropic tissue, i.e. its mechanical properties vary depending on the loading directions. Pinilla *et al.* (1996) have experimentally shown that the structural capacity of the proximal femur is sensitive to slight variations in the loading direction. Moreover, due to the heterogeneity of bone, there may be regions characterized by a different structure where the bone is weaker and consequently is more likely to fail (Eckstein *et al.* 2002, Perilli *et al.* 2008). Finally, bone is a viscoelastic material, i.e. its mechanical properties are strain-rate dependent. Therefore, the loading speed/rate affects the strength values measured (Courtney *et al.* 1994). Due to its viscoelasticity, bone can resist higher stress levels with similar strains if the strain-rate increases.

2.4 Failure of bone

The deterioration of bone mechanical competence as a result of age- or disease-related changes leads to a higher risk of bone failure. The factors associated with bone mechanical competence are affected by the rate of bone turnover (Currey 2001). In some situations this rate can not keep up the normal structure of bone and fracture may occur (Frost 1990). In addition, the structure has basically well adapted to customary, functional loadings, but not to unusual loadings caused by occasional falls or by other trauma-related events (Currey 2003, Sievänen *et al.* 2007a).

It is axiomatic that a fracture occurs when the load concentrated on the bone exceeds the strength of the bone (Currey 2001). Thus, fracture risk may be seen to be straightforwardly dependent on bone strength. However, the fracture is not an event involved by only a single or some certain reasons, but the aetiology of fractures is much more complicated. The aetiology of any type of fracture is multifactorial involving also many extra-skeletal risk factors (Kanis 2002, Fyhrie 2005, Järvinen *et al.* 2005, Sambrook & Cooper 2006, Sievänen *et al.* 2007a, Cheung & Detsky 2008, Järvinen *et al.* 2008). This background is discussed in the next section.

2.4.1 Fracture risk

It has been generally accepted that the assessment of fracture risk should encompass all aspects of risk (Kanis 2002, Sambrook & Cooper 2006). In other words, all factors related to the “situation in which bone usually breaks in life” (Currey 2002) should ideally be taken into account.

According to this strategy, numerous clinical and experimental studies have recently been published, where several risk factors related to bone mechanical competence as well as extra-skeletal risk factors associated with the increasing risk of fracture have been identified. In general, structure-related risk factors of fracture can be associated with the factors that affect bone mechanical competence. These include bone macroarchitecture (shape and geometry), bone microarchitecture (trabecular bone structure), matrix and mineral composition as well as the degree of mineralization, microdamage accumulation, and the rate of bone turnover, which can affect the structural and material properties of bone (Sambrook & Cooper 2006). The central ones of these factors (often referred to as bone quality in the literature) have been presented in the context of bone mechanical competence. Here, a more specific review of the clinical evidence of their contribution to the fracture risk will be given.

In some context, BMD (bone mass) is also included among the structure-related risk factors, whereas in another usage all structural characteristics of bone refer to the influence of factors that affect fracture risk but are not accounted for by bone mass (Hernandez & Keaveny 2006). Here, reduced bone mass (osteoporosis) is discussed as a separate, single risk factor of fracture. The extra-skeletal risk factors and their contribution to fracture risk are also described below.

Osteoporosis

Osteoporosis is a complex skeletal disease with a multifactorial background. It is characterized by reduced bone density (i.e. bone loss) and the deterioration of bone architecture resulting in the increase of bone fragility and consequently susceptibility to fracture (Anonymous 1993).

The clinical diagnosis of osteoporosis is typically based on the measurements of areal BMD by dual-energy X-ray absorptiometry (DXA)¹. The WHO has

¹ The DXA methodology will be discussed in more detail in the context of the clinical assessment of fracture risk (chapter 2.5.1).

established the diagnostic criteria for osteoporosis on the basis of BMD T-scores. The WHO uses a threshold level of -2.5 standard deviation (SD) or below the mean of young adult women as the criterion of osteoporosis (T-score \leq -2.5) (Anonymous 1994). However, the choice of reference value for the calculation of the T-score is not consistent in the literature due to the availability of multiple different reference databases. It is also well-known that several things affect BMD and/or T-score values. Absolute BMD varies between populations that come from different geographical regions, BMD values are dependent on the DXA device used and the T-score values are critically affected by the reference BMD and SD values used. To avoid these flaws and improve the harmonization of diagnostic classification, the use of the universal reference NHANES III database has recently been suggested (Kanis *et al.* 2008b). Manufacturers of bone densitometry devices have also been moving from manufacturer-specific reference values to these data. Because the NHANES III data have been acquired using Hologic densitometers, conversion equations for standardizing BMD values have been published. These equations thereby allow for their use with other densitometers. (Hanson 1997, Genant *et al.* 1994, Lu *et al.* 2001.) Anyway, the standardization processes for osteoporosis diagnosis and the assessment of fracture risk are still in progress, and it seems obvious that the need for “the development of new techniques with higher performance characteristics than BMD or that add significant information to BMD” remains (Kanis *et al.* 2008b).

The pathogenesis of osteoporosis is complex and partly unknown. A major determinant of bone density in older age is the peak bone mass reached at young age (Cooper & Melton 1992, Mora & Gilsanz 2003). Later in life, bone resorption may begin to dominate over formation. The imbalance in the bone turnover process causes bone loss, taking place especially as a result of estrogen deficiency in postmenopausal women. Estrogen has a central role in normal physiological remodelling, and its deficiency after the menopause results in a remodelling imbalance with a substantial increase in bone turnover, leading to progressive bone loss. Although osteoporosis is typically associated with postmenopausal women, bone loss and the deterioration of bone structure may also happen in immobilization, some diseases (e.g. secondary hyperparathyroidism, Paget’s disease), or pharmaceutical interventions (e.g. long-term cortisone treatment). (Ganong 2005, Lane 2006, Sambrook & Cooper 2006)

Osteoporosis is considered to be an important public health issue because of its high social and economical burden, i.e. because of the high number of fragility fractures that are associated with the outcome of the disease. The problem is

increasing steadily in consequence to the ageing of the world population. (Cummings & Melton 2002) It has been estimated that there are over 400 000 persons in Finland that suffer from osteoporosis. It has also been estimated that osteoporosis currently affects more than 10 million people in the United States, and the disease is projected to impact approximately 14 million adults over the age of 50 by the year 2020 (Lane 2006). Worldwide, approximately 200 million women have osteoporosis. Although the likelihood of developing the disease is currently the greatest in North America and Europe, it will increase in the developing countries as population longevity continues to increase. (Lane 2006)

Osteoporosis is thought to be the most prevalent cause of increasing bone fragility and consequently fracture risk. Evidence that the risk of fracture increases as BMD declines has been shown in numerous epidemiological studies (Cummings *et al.* 1993, Marshall *et al.* 1996, Schott *et al.* 1998, Johnell *et al.* 2005). For example, it has been shown that each SD decrease in femoral neck BMD increased the age-adjusted risk of hip fracture 2.6 times (Cummings *et al.* 1993). In the same study, it was also shown that women with BMD in the lowest quartile had an 8.5-fold greater risk of hip fracture than those in the highest quartile.

Although osteoporosis is one important risk factor for a fracture, recent studies have clearly shown that all individuals with low BMD do not sustain a fracture (Marshall *et al.* 1996, Wilkin & Devendra 2001, Kanis 2002, Kaptoge *et al.* 2005). On the other hand, the majority of hip fractures occur among people who can not be classified as having osteoporosis using the DXA-based BMD T-score threshold value of -2.5 (Stone *et al.* 2003, Schuit *et al.* 2004). However, only little attention has been paid to these individuals with higher BMD. It is possible that only very low DXA-based BMD has the capacity to explain whether or not a fracture will occur, whereas other risk factors may be associated with hip fracture in patients with higher BMD. The fact that the ability of BMD to predict fracture occurrence is limited (Stone *et al.* 2003, Schuit *et al.* 2004, Robbins *et al.* 2005) provides support for this issue. Anyway, it is important to keep in the mind that osteoporosis is only one single risk factor for a fracture. Fracture risk is dependent on the bone strength, which is determined not only by BMD but also by several other factors that will be discussed next.

Structure-related risk factors

The proximal femur is a complex structure, and identifying specific measurable characteristics that reflect its strength is challenging. Although the deterioration of bone structure is typically associated with osteoporosis, we have however indisputable evidence that there are several structural factors that contribute to bone mechanical competence and consequently to fracture risk, independently of BMD (Legrand *et al.* 2000, Benhamou *et al.* 2001, Partanen *et al.* 2001, Chappard *et al.* 2005, El-Kaissi *et al.* 2005, Gnudi *et al.* 2004, Gregory *et al.* 2005, Faulkner *et al.* 2006, Szulc *et al.* 2006, Sievänen *et al.* 2008).

The large variation in the mechanical behaviour of bone is associated with geometrical variation. Several geometrical measures of hip structure have been suggested as possible risk factors for hip fracture. Increased femoral neck axis length (FNAL) or hip axis length (HAL), wide neck-shaft angle (NSA), and narrow femoral neck width have often been considered as independent risk factors for hip fracture (Table 3), even if the findings are not fully consistent (Karlsson *et al.* 1996, Duboeuf *et al.* 1997, Center *et al.* 1998, Alonso *et al.* 2000, Partanen *et al.* 2001, Bergot *et al.* 2002, Gnudi *et al.* 2002, Gnudi *et al.* 2004, Faulkner *et al.* 2006). Sievänen *et al.* (2007b) have evaluated proximal femur macroanatomy of medieval and contemporary adults and shown that within 1000 years the femoral neck axis has become longer and its cross-section has become proportionally smaller and more oval in shape. In addition, NSA showed a consistent secular increase of about 4 degrees. The authors conclude that these changes in the present external phenotype alone account for about 50% higher fall-induced stress compared with the medieval situation (Sievänen *et al.* 2007b). Furthermore, it has been shown that the cortical thickness is reduced in patients with hip fracture, suggesting its potential role as a risk factor of fracture (Glüer *et al.* 1994, Partanen *et al.* 2001, Gnudi *et al.* 2002, Szulc *et al.* 2006). There is evidence that especially the thinning of a superolateral femoral neck cortex with age leads to the loss of elastic stability due to underloading of this site in the normal loading conditions (standing position, walking), exposing consequently the local buckling of the cortex (Mayhew *et al.* 2005, Rivadeneira *et al.* 2007). This finding is also supported by a recent longitudinal study, in which the loss of cortical bone was shown to occur because of substantial endocortical resorption in comparison with insufficient periosteal apposition (Lauretani *et al.* 2008).

Bone fragility and susceptibility to fracture are increased not only due to changes in bone geometry, but also to the resorption of trabecular bone. The

changes in bone microstructure, loss of connectivity and removal of trabeculae can significantly decrease bone strength and increase the susceptibility to fracture (Eriksen *et al.* 1990, Silva & Gibson 1997, Legrand *et al.* 2000, Benhamou *et al.* 2001, Chappard *et al.* 2005, Felsenberg & Boonen 2005, Hudelmaier *et al.* 2005, Hernandez & Keaveny 2006). In fact, the key role of trabecular bone structure with regard to the fracture risk was suggested by the classic definition of osteoporosis adopted in 1993 (Anonymous 1993). Indeed, several authors have reported the successful identification of osteoporotic patients from controls using texture analysis of trabecular bone derived from radiographs (Pothuau *et al.* 1998, Benhamou *et al.* 2001, Gregory *et al.* 2004, Chappard *et al.* 2005, Vokes *et al.* 2006). More importantly, some studies have demonstrated that the parameters aimed to quantify trabecular bone structure can also distinguish fracture cases from controls independently of BMD. For example, marked alterations of trabecular number, spacing, trabecular bone connectivity, fractal dimension, and anisotropy have been reported in patients with vertebral or hip fracture compared with control subjects (Table 3) (Legrand *et al.* 2000, Benhamou *et al.* 2001, Gregory *et al.* 2004, Chappard *et al.* 2005, Vokes *et al.* 2006).

Table 3. The reported values of structural variables in fracture patients and controls.

Variable	Fracture patients	Controls	p-value	Author
Geometrical variables				
HAL (cm)	10.9 ± 0.7 ^(a)	10.7 ± 0.6	0.01	Gnudi <i>et al.</i> (2002)
NSA (degrees)	133.7 ± 6.9 ^(a)	128.3 ± 4.8	<0.001	Partanen <i>et al.</i> (2001)
ND (cm)	3.08 ± 0.02 ^(a)	3.01 ± 0.004	< 0.002	Rivadeneira <i>et al.</i> (2007)
FNC (mm)	1.22 ± 0.18 ^(a)	1.31 ± 0.19	<0.005	Szulc <i>et al.</i> (2005)
Trabecular variables				
Connectivity	3.83 ± 2.8 ^(b)	2.2 ± 0.9	0.01	Legrand <i>et al.</i> (2001)
Trabecular number (1/μm)	1.2 ± 0.4 ^(b)	1.4 ± 0.3	0.002	Legrand <i>et al.</i> (2000)
Trabecular spacing (μm)	806.9 ± 275.9 ^(b)	653.3 ± 189.1	0.005	Legrand <i>et al.</i> (2000)
Degree of anisotropy	1.76 ± 0.16 ^(b)	1.55 ± 0.14	<10 ⁻⁴	Chappard <i>et al.</i> (2005)
Fractal parameter	0.67 ± 0.06 ^(a)	0.70 ± 0.03	0.003	Benhamou <i>et al.</i> (2001)

^(a) Hip fracture; ^(b) Vertebral fracture

Even though we have indisputable evidence that both bone geometry and trabecular bone structure are important risk factors for a fracture and that the assessment of structure-related characteristics improves the prediction of fracture risk, we have a lack of data about their combined contribution to the risk of fracture. This aspect may have a special importance in skeletal sites in which both

morphologically different bone types are present. Altogether, much additional work will be needed to identify and standardize the specific structural parameters that are optimal for the assessment of bone fragility and finally for the prediction of fracture risk.

Extra-skeletal risk factors

In addition to the factors related to the mechanical competence of bone, several extra-skeletal risk factors associated with the increased risk of fracture have been established. These factors include clinical, medical, behavioural, nutritional and genetic variables that interact more or less with each other (Table 4 and Table 5) (Kanis 2002, Kanis *et al.* 2005, Lane 2006).

Table 4. Extra-skeletal risk factors for a fracture. Adopted from Kanis (2002), Kanis *et al.* (2005) and Lane (2006).

Clinical factors	Medical factors	Nutritional factors	Genetic factors	Behavioural factors
Low BMD	Glucocorticoid therapy	Low calcium intake	Female sex	Cigarette smoking
Age	Premature menopause	Vitamin D efficiency	Asian or white ethnic origin	Low level of physical activity
Previous fragility fracture	Poor visual acuity	Excessive alcohol consumption	Body size	
Family history of hip fracture	Rheumatoid arthritis	Excessive caffeine consumption		
Low bodyweight	Neuromuscular disorder			
Increased risk of falling	Long-term immobilization			

Table 5. Risk ratio for hip fracture associated with risk factors adjusted for age, with and without adjustment for BMD. Adopted from Kanis *et al.* (2005).

Risk indicator	Without BMD		With BMD	
	RR	95% CI	RR	95% CI
Body mass index (20 vs. 25 kg/m ²)	1.95	1.71-2.22	1.42	1.23-1.65
Body mass index (30 vs. 25 kg/m ²)	0.83	0.69-0.99	1.00	0.82-1.21
Prior fracture after 50 years	1.85	1.58-2.17	1.62	1.30-2.01
Parental history of hip fracture	2.27	1.47-3.49	2.28	1.48-3.51
Current smoking	1.84	1.52-2.22	1.60	1.27-2.02
Ever use of systemic corticosteroids	2.31	1.67-3.20	2.25	1.60-3.15
Alcohol intake > 2 units daily	1.68	1.19-2.36	1.70	1.20-2.42
Rheumatoid arthritis	1.95	1.11-3.42	1.73	0.94-3.20

Probably the most noteworthy extra-skeletal (clinical) risk factor of fracture is the risk of falling. The recent data indicate that falls are a stronger predictor of fracture than BMD (Kaptoge *et al.* 2005). Other studies have also suggested that instead of osteoporosis, falling is the strongest single risk factor for a fracture, and the type and severity of falling are crucial in determining whether a fracture occurs (Hayes *et al.* 1993, Nevitt & Cummings 1993, Dargent-Molina *et al.* 1996, Schwartz *et al.* 1998, Wei *et al.* 2001, Robinovitch *et al.* 2003). A sideways fall increases the risk of hip fracture three to five times, and the risk is even 30-fold if there is a direct impact to the hip (Robinovitch *et al.* 2003). A fracture is usually related to reduced bone strength and falling, alone or more often in combination. In persons aged 65 years or over, falls are the main aetiological factor in over 90% of hip fractures, and a history of falls is associated with an increased risk of hip fractures (Cumming & Klineberg 1994, Cummings *et al.* 1995, Geusens *et al.* 2002). Thus, it is not surprising that the focus in fracture prevention has recently been suggested to shift from osteoporosis to falls (Järvinen *et al.* 2008).

2.4.2 Hip fractures

Hip fractures have been considered to be the most serious outcome of osteoporosis (Cummings & Melton 2002), and they are the most common reason for acute orthopaedic admission in older people (Parker & Johansen 2006). Mortality associated with a hip fracture is about 5–10% after one month, and after one year from the fracture about a third of the patients will have died, compared with an expected annual mortality of about 10% in the same age group (Parker &

Johansen 2006). Moreover, half of those who survive will require prolonged expensive care (Ganong 2005).

Hip fracture types

Hip fractures can be radiographically classified into intracapsular (cervical or femoral neck) and extracapsular (trochanteric) fractures (Fig. 4). These may further be divided into subgroups depending on the level of the fracture and the presence or absence of displacement and comminution (Parker & Johansen 2006).

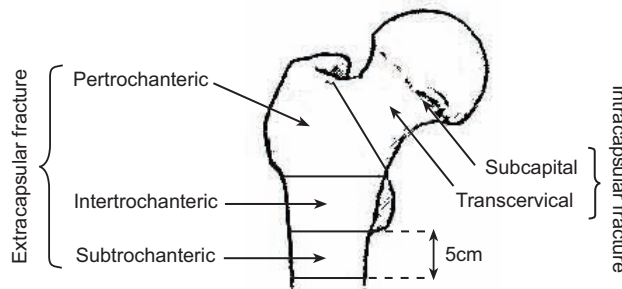


Fig. 4. The classification of hip fractures into intracapsular (cervical or femoral neck) and extracapsular (trochanteric) fractures.

The differences in the morphology of hip fractures have been reported (Kannus *et al.* 1996, Martinez *et al.* 2001, Lofman *et al.* 2002). In the review of 15 published reports Baudoin *et al.* (1993) presented that in women the ratio of cervical to trochanteric fractures evolves in three periods: 1) before the age of 50 years the incidence of cervical fractures is close to that of trochanteric fractures; 2) between 50 and 60 years of age cervical fractures increase markedly and the cervical to trochanteric ratio is well above unity at an age when the fracture incidence is still very low; and 3) this imbalance progressively diminishes to reach unity in the very old as a result of a progressive increase in trochanteric fractures. In men, cervical fractures are progressively more common with increasing age, and the cervical to trochanteric ratio exceeds unity after 70 years of age.

Epidemiological studies have suggested that trochanteric fractures are an increasing problem compared with cervical fractures since their relative number increases progressively with age in women over the age of 60 years and since their incidence has been shown to increase in both sexes and all age groups during

the recent decades (Kannus *et al.* 1996, Lofman *et al.* 2002). Also, trochanteric fractures have been associated with increased mortality compared with femoral neck fractures (Haentjens *et al.* 2007).

Epidemiology

In general, the worldwide cumulative rate of low-energy fractures (“osteoporotic fractures”) is very high; in white populations, about 50% of women and 20% of men older than 50 years of age will have a fragility fracture in their remaining life (Sambrook & Cooper 2006). Global numbers of hip fractures were reported as 1.3 million in 1990 (Parker & Johansen 2006), and it has been estimated that the total number will increase to 2.6 million by the year 2025 and to 4.5 million by the year 2050 worldwide (Gullberg *et al.* 1997). It has been estimated by Kannus *et al.* (1999) that if the rather linear development in the incidence of hip fractures continues, the total number of hip fractures in the elderly in Finland is about 7850 in the year 2000, and will be even 19 000 in the year 2030. Lönnroos *et al.* (2006) have reported that the total number of hip fractures has almost doubled during 10 years, between 1993 and 2003, and the age-adjusted incidence rate increased in both sexes. On the other hand, Kannus *et al.* (2006) have later updated their prediction by following the incidence of hip fractures in Finland up to year 2004. The growth trend had declined: there were about 7100 hip fractures in Finland in 2004 (Kannus *et al.* 2006). The authors stated that if the incidence of fractures were to become stabilized to the 2004 level, the number of hip fractures would be approximately 12 600 in 2030 (Kannus *et al.* 2006). A levelling off or downward trend in the incidence of hip fractures has also been reported in other studies (Rogmark *et al.* 1999, Lofthus *et al.* 2001, Martinez *et al.* 2001).

Differences in the etiopathology between hip fracture types

The majority of studies regarding the assessment of hip fracture risk ignore the classification of hip fracture type, even though different subgroups (intracapsular and extracapsular, i.e. femoral neck and trochanteric fractures) have relevance for the clinical treatment (Parker & Johansen 2006), and the predictive factors for different hip fracture types have been shown to differ (Duboeuf *et al.* 1997, Fox *et al.* 2000, Partanen *et al.* 2001, Gnudi *et al.* 2002, Szulc *et al.* 2006). Mautalen *et al.* (1996) have published a review in which they stated that the two main types of

hip fractures should be evaluated separately in order to increase both the knowledge and the future likelihood of preventing hip fractures.

Based on studies of the classification of hip fracture type, the geometrical parameters of the upper femur have been established to be important in the pathogenesis of these two main hip fracture types. Trochanteric fractures seem to be mostly a consequence of a generalized low BMD, whereas structural parameters might be involved in cervical fractures (Duboeuf *et al.* 1997, Schott *et al.* 1998, Partanen *et al.* 2001, Gnudi *et al.* 2002, Schott *et al.* 2005).

In addition to the bone-related parameters, general health status and clinical risk factors have appeared to differ between patients with different fracture types (Stewart *et al.* 1999, Fox *et al.* 2000). Altogether, all these studies establish the requirement to discriminate fracture types for both the better understanding of multifactorial etiology of different hip fracture types and finally for the relevant individual fracture risk assessment.

2.5 Clinical assessment of fracture risk

Bone mechanical strength can not be measured *in vivo*. Therefore, in order to evaluate bone mechanical competence non-invasively, it is necessary to examine clinically definable surrogates for the mechanical strength of bone, i.e. the bone-related factors that predispose to fractures.

In addition to the bone-related traits, all factors related to the “situation in which bone usually breaks in life” (Currey 2002) should ideally be taken into account in the assessment of fracture risk. Therefore, combined models have recently been suggested in which both non-invasively measurable bone-related risk factors as well as extra-skeletal risk factors associated with the increased risk of fracture are considered (Kanis 2002, Järvinen *et al.* 2005, Kanis *et al.* 2005, Lane 2006, Kanis *et al.* 2008a). The general overview of the methodology that is currently in clinical use or have been suggested to come into clinical use for assessing the risk of fracture will finally be presented in this chapter.

2.5.1 Radiologic evaluation

When the radiological techniques are used for the assessment of bone mechanical competence and consequently fracture risk, the imaging modality used should provide quantitative information on bone structure. Ideally, the method should thus be adapted to the structural characteristics of trabecular bone, i.e. the spatial

resolution of the used method should be at least similar to that of the trabeculae, and also identical in three dimensions. When these conditions were met, morphological and topological information could be obtained. In practice this means that the spatial resolution should be at least 100 μm because the trabeculae are 100–150 μm thick on average. Also, slices thicker than 500 μm do not provide direct access to the trabecular network, because trabeculae are spaced approximately 500–1000 μm apart from each other. (Lespessailles *et al.* 2006) In spite of the strict ideal conditions, the approximation for the quantitative properties of bone structure can be obtained in several methods that are currently available. The parameters are said to be apparent in situations where the ideal conditions are not met.

Several techniques for *in vivo* assessment of bone health status and consequently fracture risk have been described, including dual-energy X-ray absorptiometry (DXA), ultrasound (US), high resolution computed tomography (CT), and magnetic resonance imaging (MRI) (Link *et al.* 1998, Müller *et al.* 1998, Nicholson *et al.* 2001, Njeh *et al.* 2001, Herlidou *et al.* 2004, Hudelmaier *et al.* 2004, Hudelmaier *et al.* 2005, Bauer *et al.* 2006, Mueller *et al.* 2006, Lammentausta *et al.* 2006, Showalter *et al.* 2006). However, there are some limitations in the use of these methods due to inaccuracy (DXA, US), radiation dose (CT), availability (DXA, CT, MRI), or costs (CT and MRI). The analysis of native X-ray images has also been proposed for measuring both bone geometry and structure (Pothuaid *et al.* 1998, Lin *et al.* 1999, Benhamou *et al.* 2001, Chappard *et al.* 2001, Veenland *et al.* 2002, Gregory *et al.* 2004, Chappard *et al.* 2005, Guggenbuhl *et al.* 2006, Vokes *et al.* 2006). The brief comparison of radiological methods used currently in *in vivo* fracture risk assessment is given in Table 6 and the more detailed description of these methods will also be presented in this section.

Table 6. Comparison of radiological methods used currently in the clinical assessment of hip fracture risk.

Method	Resolution (nominal)	Available parameters	Typical effective dose (μSv)*
DXA	$> 1 \times 1 \text{ mm}^2$	BMD, whole bone morphology (NSA, HAL)	1–20
QUS	–	BUA and SOS (reflect the qualitative mechanical properties of bone), cortical thickness	–
QCT	$400 \times 400 \times 1000 \text{ }\mu\text{m}^3$	BMD, morphology, trabecular architecture, porosity, cortical thickness	50–1000 (BMD) 1000–10000 (imaging)
MRI	$200 \times 200 \times 500 \text{ }\mu\text{m}^3$	Morphology, trabecular architecture, porosity, cortical thickness	–
Radiography	film: $40 \times 40 \text{ }\mu\text{m}^2$ digital: $100 \times 100 \text{ }\mu\text{m}^2$	Morphology, trabecular architecture, porosity, cortical thickness	1000–2000

DXA, dual-energy X-ray absorptiometry; QUS, quantitative ultrasound; QCT, quantitative computed tomography; MRI, magnetic resonance imaging; NSA, neck-shaft angle; HAL, hip-axis length; BUA, broad-band ultrasound attenuation; SOS, speed of sound; * For comparison, the daily background radiation dose is approximately 10 μSv

DXA

Prior to 1993, osteoporosis was defined by the presence of a fragility fracture (Cheung & Detsky 2008). With the launch of DXA to measure BMD, the WHO established a new definition of osteoporosis based on BMD T-scores (Anonymous 1993, Anonymous 1994). Since those days the benchmark for the assessment of fracture risk has been the status of osteoporosis based on the measurement of BMD by DXA and clinicians still rely on it for the fracture risk assessment and treatment decisions (Cheung & Detsky 2008).

A major advantage of DXA is that the radiation dose of measurements is low. The effective dose of an adult from a spine and hip examination is between 1 and 20 μSv depending on the make, model and scan mode used, which is approximately equivalent to the daily background radiation exposure (Njeh *et al.* 1999). Another advantage of the method is a good precision of measurements, with the CV % being 1–2% (Fogelman & Blake 2000).

DXA is able to account for variations in the amount of overlying soft tissue by measuring the attenuations of X-ray beams at two distinct energies. DXA,

however, is prone to several inaccuracies. DXA is a projectional method, and can thus provide a two-dimensional picture of the target. Consequently, the DXA-based BMD represents areal BMD rather than true volumetric BMD. In addition, the size of bone as well as the scan projection affects the density values measured, i.e. the larger the bone, and the thicker the bone in the scan direction, the higher the BMD value measured. (Sievänen 2000, Bolotin & Sievänen 2001) In fact, DXA can provide information on the amount of bone (bone mass), not on density that has a clear physical meaning in reality. As regards the structural determinants of bone (bone size, geometry, internal architecture etc.), DXA is unable to resolve these, and BMD is thus confined to remain an integral measure only. On the other hand, this integral nature of BMD can improve its ability to predict fracture, since bone size is also a determinant of bone strength. (Sievänen 2000) It is also noteworthy that DXA-based BMD T-scores were determined for the estimation of the prevalence of osteoporosis across populations, not for the assessment in specific patients (Faulkner *et al.* 1999).

In recent studies, DXA has been shown to lack the predictive ability with regard to the individual risk of fracture (Wilkin & Devendra 2001, Kanis 2002, Stone *et al.* 2003, Schuit *et al.* 2004). It has also been found that patient-specific DXA-measured *in vivo* BMD inaccuracies as high as 20% or more can be readily anticipated clinically, and they may thus compromise patient-specific evaluation of fracture risk (Bolotin *et al.* 2001).

In response to these well-known limitations of DXA, manufacturers have developed the devices to enhance the ability of DXA-method to predict fractures. Novel DXA devices include the possibility to measure some geometrical parameters, such as HAL and NSA. Also, hip structural analysis (HSA) has been developed to derive the cross-sectional geometry of femoral neck from raw bone mineral image data for an estimate of hip strength (Beck *et al.* 1990, Beck *et al.* 2000). However, due to the planar original image, the approach provides only a rough estimate of structural indices (Duan *et al.* 2003). Moreover, because of the strong correlations between BMD and structural parameters, it is not clear yet whether HSA can provide additional information about the clinical fracture risk assessment (Melton *et al.* 2005). However, it is possible that three-dimensional data can be captured by DXA in the future since the devices enabling three dimensional imaging are under development.

Ultrasound

An image of bone structure can not be produced by ultrasound measurements, although a measurement site can already be located based on imaging by novel ultrasound devices (Falgarone *et al.* 2004, Kazakia & Majumdar 2006). However, the skeletal status can be assessed using quantitative ultrasound measurements (QUS) (Glüer 2007). The most widely used QUS methods are broad-band ultrasound attenuation and speed of sound (or ultrasound velocity) at the heel (Kanis 2002). Because the method does not involve ionising radiation there is much interest in launching QUS in clinical use.

QUS of the heel has been suggested to yield information about the qualitative mechanical properties of bone and bone structure in addition to bone mass (Nicholson *et al.* 2001, Njeh *et al.* 2001, Portero *et al.* 2005). QUS can discriminate healthy persons from osteoporotic patients, although a significant false negative rate has been detected (Moyad 2003, Kazakia & Majumdar 2006). In addition, validated heel QUS devices predict fragility fracture in postmenopausal women (hip, vertebral, and global fracture risk) and men over the age of 65 years, independently of central DXA BMD (Hans *et al.* 1996, Bauer *et al.* 1997, Cheng *et al.* 1997a, Schott *et al.* 2005, ISCD 2007, Lewiecki *et al.* 2008). However, the technique can not be used to diagnostic purpose yet. It is appropriate for screening, but the diagnosis has to be confirmed by the DXA measurements (Kazakia & Majumdar 2006). Heel QUS in conjunction with clinical risk factors can be used to identify a population at very low fracture probability in which no further diagnostic evaluation may be necessary (ISCD 2007, Lewiecki *et al.* 2008).

Altogether, QUS seems to have potential and is thus under intensive research. According to Glüer (2007), three issues have to be resolved for widespread clinical acceptance: (1) Will patients with low QUS readings benefit from approved osteoporosis medications? (2) How good quality of QUS measurements can be ensured in daily clinical practice? (3) How much added value does QUS bring to risk factor based case-finding strategies?

Quantitative computed tomography (QCT)

QCT enables us to determine the true three-dimensional structure and volumetric BMD of both trabecular and cortical bone separately, providing thus better possibility to predict bone failure (Genant *et al.* 1996, Fogelman & Blake 2000,

Bousson *et al.* 2006). The method is also precise enough to detect skeletal changes over time, and can thus be used to follow the disease state or to monitor results of therapy (Lane 2006). However, the analysis of trabecular structure is subjected to partial-volume effect, and individual trabeculae are not depicted due to the limited spatial resolution with a slice thickness of approximately 1 mm in high resolution clinical scanners (Link *et al.* 1999).

Ex vivo studies have shown that volumetric BMD measured by QCT and DXA-based areal BMD provide comparable predictive power of vertebral and radial strength (Cheng *et al.* 1997c, Ebbesen *et al.* 1999, Hudelmaier *et al.* 2004). Distinct improvements in the strength prediction have been demonstrated with the additional geometrical measurements, e.g. with the measurement of bone cross-sectional area from QCT images (Cheng *et al.* 1997c, Lang *et al.* 1997, Lotz & Hayes 1990). Compared with DXA, QCT provides similar or better results in the prediction of spinal fracture risk in postmenopausal women (Lang *et al.* 2002, Rehman *et al.* 2002). Due to limited medical evidence, measurements at the hip are not suggested until more data emerge (ISCD 2007). The radiation dose, limited availability and high cost also confine the widely clinical use of QCT (Kanis 2002, Kazakia & Majumdar 2006, Damilakis *et al.* 2007).

A recent development in QCT technology is the availability of peripheral scanners (pQCT). Newer models of pQCT scanners provide the isotropic resolution up to approximately 80 μm . In addition to the higher resolution, peripheral devices make QCT technology less expensive and more accessible than traditional whole-body scanners. Additionally, radiation dose is substantially lower in the pQCT scans compared with the central body measurements. However, the pQCT method is confined to peripheral sites, and is not thus capable of providing images or measures within the spine or the proximal femur. (Kazakia & Majumdar 2006)

MRI

MRI is a three dimensional imaging method, which is based on the imaging of the relaxation properties of excited hydrogen nuclei. Thus, it does not use ionising radiation, which is the main advantage of the method. Imaging cost and the availability of the MRI scanners, however, confine the widely clinical use of the MRI.

Clinical high-resolution MRI scanners have recently achieved sufficient spatial resolution to quantify the parameters of trabecular bone (Newitt *et al.* 2002,

Wehrli *et al.* 2006), including apparent bone volume fraction, trabecular thickness, trabecular number and trabecular separation. At present, nominal in-plane spatial resolution is approximately 200 μm and slice thickness is 300–700 μm in *in vivo* MRI. Therefore, MRI can be used to detect differences in the trabecular structure with age, BMD, and osteoporosis status. (Lespessailles *et al.* 2006, Kazakia & Majumdar 2006) Texture measures computed from MR images have been shown to have similar capability to predict the elastic modulus of bone than those of parameters derived from CT images (Link *et al.* 1998). In predicting the existence of vertebral fractures, it has been shown that distal radius MR images perform better than DXA scans of the same region (Wehrli *et al.* 1998). However, there is still only little evidence about the ability of MRI to predict fractures. The methodology is currently under intensive research and the introduction of new MRI devices characterized by a stronger magnetic field and of new sequences for rapid acquisition will continue to evolve (Lespessailles *et al.* 2006).

Radiography

Since conventional radiography is widely available and imaging costs are low, it has been of considerable interest to discover how well the mechanical competence of bones can potentially be determined using this technology. As early as 1960, radiogrammetry was one of the first attempts to quantify the macroscopic structure of bone based on the measurements of the cortical thickness of the metacarpals from plain radiographs (Barnett & Nordin 1960). In 1970, Singh *et al.* described an index for the degree of osteoporosis by assessing changes in the trabecular pattern of the proximal femur by visual inspection of radiographs (Singh *et al.* 1970). They obtained a high correlation ($r = 0.81$, $p < 0.001$) between the radiological and histological assessment of osteoporosis. Today, a computer aided application for determining the Singh index is also available (Smyth *et al.* 1997). Glüer *et al.* (1994) have furthermore shown that simple measurements based on pelvic radiographs predicted fractures equally well as hip bone density.

Even if native radiography is a projectional imaging modality, it can be utilized to analyze both trabecular structure and bone geometry due to the sufficient spatial resolution of images. Conventional radiographs have a resolution of up to 40 μm when a high-resolution mammography-type film is used (Lespessailles *et al.* 2006). In the novel digital radiography, the nominal resolution is however lower, being approximately 100–150 μm .

Several authors have reported the successful identification of osteoporotic patients from controls using texture analysis of trabecular bone derived from radiographs (Pothuau *et al.* 1998, Benhamou *et al.* 2001, Gregory *et al.* 2004, Chappard *et al.* 2005, Vokes *et al.* 2006). In addition, the results obtained from the analysis of plain radiographs have been shown to be reproducible and to correlate with biomechanical properties (Lespessailles *et al.* 1998a, Millard *et al.* 1998) and with a number of histological characteristics of bone (Lespessailles *et al.* 1998b). Benhamou *et al.* (2001) have also shown that fractal analysis of radiographic trabecular bone can yield complementary information to BMD in the prediction of fractures. However, radiographic imaging produces relatively high radiation dose, which has to be taken into account in the clinical imaging situations.

The basic methodological difficulty of radiography is that the image acquisition conditions can cause intensity and contrast variations between images, which make it difficult to evaluate bone structure or density accurately. Even if the standardization of exposure parameters is used, gray-level analysis of X-ray films reflects the bone mass poorly. Thus, advanced image analysis methods must be applied to obtain the relevant structural information on trabecular bone.

A radiograph represents the 2-D projection of trabecular pattern and can be considered as a texture. Thus, several texture analysis methods have been proposed for the purpose of trabecular bone quantification (Pothuau *et al.* 1998, Lin *et al.* 1999, Benhamou *et al.* 2001, Chappard *et al.* 2001, Veenland *et al.* 2002, Gregory *et al.* 2004, Chappard *et al.* 2005, Guggenbuhl *et al.* 2006, Vokes *et al.* 2006). Texture analysis techniques are based either on mathematical morphology or on fractal geometry. Mathematical morphology generally requires image binarization, typically performed by thresholding. This may lead to a loss of information. In fractal analysis, there is a limitation since the trabecular pattern is not clearly fractal in nature. Veenland *et al.* (1996) concluded that only when using the same object-focus distance, the same X-ray exposure conditions and the same digitizer at the same resolution, can fractal dimensions be reliably compared.

Despite the challenges related to the imaging modality, radiological texture analysis can be readily used in vast populations (Lespessailles *et al.* 2006), which increases the interests to develop new radiographic-based methods for the assessment of fracture risk. Moreover, the increased computation power of novel computers provides a good possibility to develop more sophisticated imaging analysis techniques for the assessment of bone mechanical competence and fracture risk.

2.5.2 Clinical risk factors

The choice of clinical risk factors to be used in the fracture risk prediction depends not only on their predictive capability but also on their ease of clinical application (Kanis *et al.* 2005). In general, clinical risk factors scores have shown relatively poor specificity and sensitivity to predict either BMD or fracture risk (Cummings *et al.* 1995, Johnell *et al.* 1995). Moreover, some of these risk factors vary in importance according to age. For example, risk factors for falling (e.g. visual impairment, reduced mobility and treatment with sedatives) are more strongly predictive of fracture in the elderly than in younger individuals. (Kanis 2002, Kanis *et al.* 2005)

Clinical risk factors can however provide complementary information on other methods for risk assessment purposes. Indeed, the consideration of such risk factors can be used to enhance a case finding strategy (Kanis *et al.* 2005). Recently, the WHO has launched a fracture risk assessment tool (FRAX™) with the use of clinical risk factors of fracture with and without the use of femoral neck BMD (Kanis *et al.* 2008a). The clinical risk factors included in FRAX™, identified from previous meta-analyses, comprise the body mass index, a prior history of fracture, a parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking, and alcohol intake of 3 or more units daily. The FRAX™ comprises the ten-year probability for hip fracture and for other major osteoporotic fractures with and without BMD (Table 7).

The WHO's fracture risk assessment tool has already encountered criticism, since it totally ignores some well-established general risk factors (Cheung & Detsky 2008, Järvinen *et al.* 2008). For example, falling, as the strongest risk factor for a fracture among older people (Hayes *et al.* 1993, Nevitt & Cummings 1993, Dargent-Molina *et al.* 1996, Schwartz *et al.* 1998, Wei *et al.* 2001, Robinovitch *et al.* 2003, Kaptoge *et al.* 2005), has been ignored in the FRAX™, even if the risk for falling could be clinically evaluated (Järvinen *et al.* 2008). Anyway, although this novel, long-awaited instrument has limitations, it is a substantial improvement over using the sole BMD in the fracture risk prediction and as the criterion for initiating therapy (Cheung & Detsky 2008).

Table 7. Ten-year probability (%) of a major osteoporotic fracture or hip fracture in men and women aged 65 years according to the presence of a single clinical factor. Adopted from Kanis *et al.* (2008a).

	Without BMD				T-score -2.5 SD			
	Men		Women		Men		Women	
	Osteoporotic*	Hip	Osteoporotic*	Hip	Osteoporotic*	Hip	Osteoporotic*	Hip
No clinical risk factors	4.9	0.8	8.6	1.3	9.8	3.6	12.4	3.0
Parental history of hip fracture	9.3	1.0	16.0	1.7	16.5	3.7	22.1	3.2
Current smoking	5.1	1.1	9.2	1.9	11.0	5.6	13.7	5.1
Alcohol intake >2 units daily	6.0	1.2	10.4	2.0	12.5	5.4	15.4	4.6
Rheumatoid arthritis	6.8	1.4	11.7	2.3	12.8	5.0	16.1	4.3
Oral glucocorticoids	7.5	1.5	13.7	2.7	15.0	6.1	19.7	5.5
Previous fragility fracture	9.6	1.9	16.4	3.2	16.0	5.9	20.2	5.0

* Hip, clinical spine, humeral or forearm fracture

2.5.3 Laboratory assessment

Factors associated with bone mechanical competence are affected by the rate of bone turnover (Currey 2001). Consequently, the biochemical markers of bone turnover have been used in clinical research to represent the products of bone formation and resorption that are released into the circulation. Quantitative changes in markers reflect the dynamic process of bone metabolism. (Lane 2006)

Bone metabolic markers have typically been classified into bone formation and bone resorption markers. It has been shown, for instance, that in postmenopausal women bone formation and resorption markers are significantly higher than those of premenopausal women, reflecting high bone turnover rate and associated bone loss that occur with estrogen deficiency (Garnero *et al.* 1996). In contrast, decreasing osteoclasts activity is associated with a decrease in bone turnover markers and an increase in BMD in postmenopausal women (Harris *et al.* 2001, Eastell *et al.* 2003). Biochemical markers of bone resorption have also been associated with increased vertebral and non-vertebral fractures independently of BMD. However, their use in predicting fracture risk in specific patients has not

clearly been defined. Most of the bone metabolic markers are also present in other tissues and may therefore be influenced by non-skeletal factors (Delmas *et al.* 2000). The current potential uses of biochemical markers include the ability to monitor drug efficacy and to predict increases in the bone mass, but the value of these markers in the assessment of fracture risk is likely to be in combination with other risk factors (Lane 2006).

3 Purpose of the study

The general aim of this study was to investigate the radiograph-based structural factors that predispose to hip fracture. The study has focused on combining the structural impacts of the upper femur for the assessment of bone mechanical competence and fracture risk. In addition, the behaviour of different hip fracture types was elucidated in order to test the hypothesis that cervical and trochanteric hip fractures have different explanatory factors. The specific aims of this study were:

1. To evaluate the combination of radiograph-based geometry of the upper femur and DXA measurements in the prediction of hip fracture *in vivo*.
2. To study whether the bone geometrical measurements *in vivo* can improve the assessment of hip fracture risk in subjects diagnosed not to have osteoporosis.
3. To experimentally clarify the incidence of different fracture types in different failure load levels, and to clarify the differences of bone geometry in cervical and trochanteric fractures between low and high failure loads.
4. To develop a computer-based image analysis method for the assessment of trabecular bone structure, and to clarify if the combination of geometrical and structural properties of bone is able to predict experimental failure load.

4 Materials and methods

The materials and methods used in the study series are summarized in Table 8.

Table 8. Summary of the materials and methods used in the studies.

Study	Materials	Methods	Determined parameters
I	74 hip fracture patients (all females)	DXA	BMD (FEBMD, WABMD, TRBMD)
	49 with cervical fracture	Radiography	Geometrical parameters (FSC, FNC, CFC, FSD, ND, HD, AW, TW, FNAL, HAL, NSA)
	25 with trochanteric fracture		
	40 controls (all females)		
II	57 hip fracture patients (all females)	DXA	BMD (FEBMD, TRBMD, FEBMD and TRBMD T-scores)
	39 with cervical fracture		
	18 with trochanteric fracture	Radiography	Geometrical parameters (FSC, FNC, FNAL, HAL, NSA)
	40 controls (all females)		
III	140 cadaver femurs (77 females, 63 males)	DXA	Total BMD
	88 with cervical fracture	Radiography	Geometrical parameters (FSC, CFC, FSD, ND, HD, TW, FNAL, NSA)
	52 with trochanteric fracture	Mechanical testing	Failure load
IV	62 cadaver femurs (34 females, 28 males)	DXA	BMD (FEBMD, TRBMD)
	44 with cervical fracture	Radiography	Geometrical parameters (FSC, CFC, FNAL, NSA), trabecular parameters (TBA, EN, HI, TMO)
	18 with trochanteric fracture		
		Mechanical testing	Failure load

FEBMD, femoral neck bone mineral density; WABMD, Ward's triangle bone mineral density; TRBMD, trochanteric bone mineral density; FSC, femoral shaft cortex thickness; FNC, femoral neck cortex thickness; CFC, medial calcar femoral cortex thickness; FSD, femoral shaft diameter; ND, femoral neck diameter; HD, femoral head diameter; AW, acetabular width; TW, trochanteric width; FNAL, femoral neck axis length; HAL, hip axis length; NSA, femoral neck-shaft angle; TBA, trabecular bone area; EN, Euler number; HI, homogeneity index; TMO, trabecular main orientation

4.1 Study subjects

The clinical data used in papers I and II has been received from the Department of Surgery, Oulu University Hospital. An access to the experimental cadaver material, used in papers III and IV, was realized by the collaboration with the Ludwig Maximilians University of Munich, Germany, which was started in 2004.

4.1.1 Clinical studies (I, II)

The study group consisted of 74 hip fracture patients (fracture group: mean age 74.2 years, range 53–84 years). Forty-nine of the patients had a cervical fracture (cervical group: mean age 73.1 years, range 53–84 years) and 25 a trochanteric fracture (trochanteric group: mean age 76.3 years, range 61–84 years). There is however some variation in the number of samples between analyses, since some of the fracture patients had missing BMD and/or geometrical measurement values (N = 10 for cervical and N = 7 for trochanteric fractures).

The control group consisted of 40 females (mean age 73.7 years, range 63–84) selected from among the clients who had bone densitometry done in a private clinic during the years 1998–1999. The exclusion criteria for the controls were hip fracture, any metabolic bone disease, and treatment with sex hormones, calcitonin, or bisphosphonates.

A written informed consent was obtained from each of the patients and controls, and the study protocol was approved by the institutional ethical committee.

4.1.2 Experimental studies (III, IV)

The femora investigated were obtained from a course of macroscopic anatomy from the Institute of Anatomy at the Ludwig Maximilians University of Munich, Germany. The sample represents the elderly population in Southern Germany. The individuals belonged to a wide range of medical and social background, but no detailed medical or social history was available. To identify specimens with bone diseases other than osteoporosis or osteopenia, biopsy specimens were taken from the left iliac crest for histology. Inappropriate individuals, i.e. individuals with bone disease other than osteoporosis or osteopenia, such as osteosarcoma, were excluded from the study.

The sample for study III consisted of 171 cadavers (86 females, mean age 81.3 years, and 85 males, mean age 78.2 years) whose left femora were used for the study (Fig. 1 in the original paper III). Here, thirty-one of the samples had a shaft failure in mechanical testing and they were excluded from the analysis. Thus, the sample size for final analyses comprised 140 cadavers (77 females, mean age 81.7 years, and 63 males, mean age 79.1 years). In some study samples, DXA scans (N = 2) or X-rays (N = 1) were unavailable. In addition, part of the bone

existed outside the image area in some radiographs, and the definition of some geometrical parameters in these samples was thus impossible.

Since site-specific BMD values were unavailable for the left femora, the sample for study IV consisted of 62 right proximal femur specimens (34 from females, age 81.6 ± 10.7 years, and 28 from males, age 77.8 ± 11.1 years).

4.2 Measurements

4.2.1 Bone mineral density

Clinical studies (I, II)

The BMD of the upper femur was measured with Lunar DPX scanner (Lunar DPX, Lunar Radiation, Madison, WI, USA) using standard measurement routines. Before the measurements, a control phantom was scanned daily. The measurement of the patients was performed 2–4 days after the fracture. BMD was measured at the sites of the femoral neck (FEBMD), Ward's triangle (WABMD) and trochanter (TRBMD) (non-fracture side of the fracture patients and left side of the controls).

Absolute BMD values were used in study I, whereas BMD T-scores were utilized in study II. BMD T-scores were calculated using the standard formula: $T\text{-score} = (\text{individual's BMD} - \text{the young-adult mean BMD}) / \text{SD of the young-adult normal population}$. Here, different reference values for the calculation of T-scores were used to test their effect on the discrimination of fracture patients and controls to osteoporotic and non-osteoporotic groups. Used reference values, summarized in Table 1 in the original paper II, were selected based on the previously published paper of Binkley *et al.* (2005), where different GE Lunar software versions and recalculated values of NHANES III database were used to study their effect on the prevalence of osteoporosis.

Experimental studies (III, IV)

In vitro DXA scans of the femora were obtained using a standard narrow fan beam scanner with multi-view image reconstruction (GE Lunar Prodigy, GE Lunar Corporation, Madison, WI, USA) with the femoral specimens submerged in a water bath. Standard positioning was utilized across all specimens. Total

femoral BMD (III) or site-specific femoral neck and trochanteric BMDs (IV) were used. All BMD values were calculated using the software provided by the manufacturer.

4.2.2 Radiography and geometrical parameters derived from radiographs

Clinical studies (I, II)

The anteroposterior pelvic roentgenograms of the fracture patients were taken within a few days postoperatively, and those of the controls were taken using the same X-ray equipment. A standard position was used in all cases: supine with the pelvis and both legs extended forward and the big toes touching each other, resulting in slight internal rotation of the femur. The beam was centered on the midline of symphysis pubis, and the focus-to-film distance was always 1 m. A calibration scale was fixed at the level of the greater trochanter of the uninvolved hip for calibrating the dimension measurements.

The radiographs were digitized with a CCD camera (Dage MTI 72E, Dage-MTI, Michigan City, IN, USA) on a light table (Northern Light Desktop Illuminator, Imaging Research, Inc., Ontario, Canada) using an objective Canon CI-TV 16 mm lens (Canon, Tokyo, Japan). The images were calibrated using the calibration scale, and the dimensions were measured with a digital image analysis system MCID M4 with the software version 3.0, revision 1.1 (Imaging Research, Inc.). Several dimensions of the uninjured hip were measured (Fig. 5). All the measurements were made by a single observer. The reproducibility of geometrical measurements was 0.9, 1.5, 2.5, 2.5, 3.3, 1.5, 0.7, 1.2, 1.1, 5.2 and 9.9% for FNALa, FNALb, FSD, TW, AW, ND, HD, HAL, NSA, FSC and FNC, respectively (Partanen *et al.* 2001).

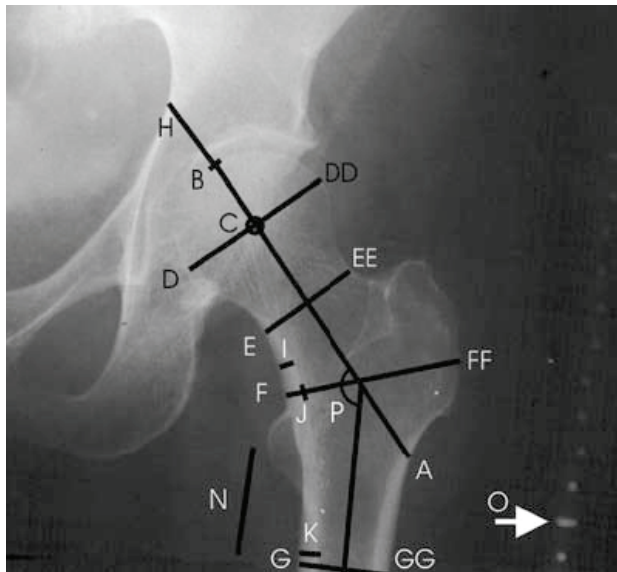


Fig. 5. Definition of the parameters measured from the anteroposterior roentgenograms of the upper femur. A-H, hip axis length (HAL); A-B, and A-C, femoral neck axis length (FNALa and FNALb, respectively, measured in two ways); B-H, acetabular width (AW); D-DD, femoral head diameter (HD); E-EE, femoral neck diameter (ND); F-FF, trochanteric width (TW); G-GG, femoral shaft diameter (FSD); I, femoral neck cortex width (FNC); J, medial calcar femoral cortex (CFC) width; K, femoral shaft cortex width (FSC); P, neck/shaft angle (NSA); O shows the calibration scale and N is a 3-cm bar generated with the software.

Experimental studies (III, IV)

The proximal femora were excised, cleaned of the surrounding soft tissue and kept moist throughout the study. The bones were radiographed with a Faxitron X-ray system (Model 43885A, Faxitron, Hewlett Packard, McMinnville, Oregon) at 40 to 85 kV, 2mA, time = 120 sec, using a 18 × 24 cm X-ray film (Agfa Structurix D7DW, Agfa, Leverkusen, Germany). X-rays were then digitized together with a calibration scale using a scanner with a resolution of 600 dpi. A set of geometrical parameters was determined from the digitized X-rays similarly to the clinical studies using Image Tool software (version 3.00, University of Texas Health Science Center, San Antonio, Texas).

4.2.3 Image processing and architectural parameters derived from processed radiographs (IV)

All image processing and analyses were performed using the Matlab® environment (The MathWorks, Inc., Natick, MA, USA). Trabecular bone was segmented from square regions of interest (ROI, 15×15 mm) by the gradient-based method, where each radiograph was first rotated, standardizing the femoral shaft axis, to obtain a uniform alignment of the images. Noise was reduced from the cropped image using a 3×3 median filter, followed by morphological top and bottom hat operations. The local gradients ∇F were calculated (Eq. 1):

$$\nabla F = \frac{\partial F}{\partial x} i + \frac{\partial F}{\partial y} j \quad (1)$$

The gradient-based gray-level image was first constructed by multiplying the original image with the gradient matrix. The corresponding binary image was then obtained by setting the gray-level to be 1 between the neighbouring positive (maximum) and negative (minimum) values of gradients (i.e. presenting bone), and 0 elsewhere (presenting marrow space). Figure 6 shows an example for the trabecular structure of the original radiographs and the processed gradient-based images.

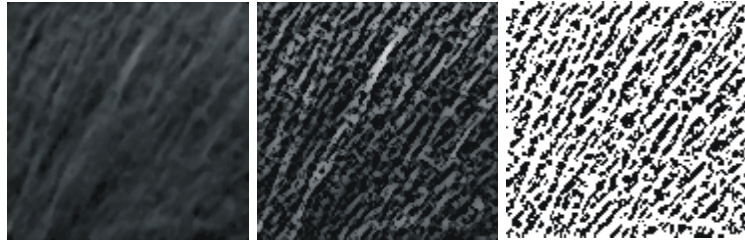


Fig. 6. Trabecular structure at the original radiographs (left) and processed gradient-based images (center). On the right, gradient-based images have been converted to binary form, white representing the trabecular bone.

After image segmentation, several structure-related parameters were calculated at the different ROIs (presented in the original paper IV, Fig. 2), which selection were based on the work of Singh *et al.* (1970), in which the distinct compressive and tensile trabecular patterns of the proximal femur are described. The summary

of the calculated variables is given in Table 9. For more detailed description of the parameters calculation, please see the original paper IV.

Table 9. Summary of the calculated trabecular parameters.

Parameter	Equation	Description
Trabecular bone area	$TBA = \sum_n \sum_n I_{n,n}$	A measure of trabecular bone mass in a gradient-based binary image I .
Homogeneity index	$HI = \sum_{i,j} \frac{GLCM(i,j)}{1+ i-j }$	A measure of the homogeneity of a structure. Calculated from co-occurrence matrix GLCM.
Euler number	EN = Number of objects - number of holes	A measure of connectivity.
Trabecular main orientation	$TMO = \arctan a \cdot \frac{180}{\pi}$	Principal orientation of trabeculae in a region of interest. Calculated from slope a of a curve, fitted to Fourier transformed binary image.

The reproducibility of the measurement of trabecular parameters was assessed by five repeated measurements of ROI 3 (original paper IV, Fig. 2) from five random radiographs, redefining the ROI each time. The reproducibility was calculated as the root mean square average coefficient of variation (RMS CV%) according to Equation 2:

$$RMSCV = \sqrt{\sum_{j=1}^n \frac{CV_j^2}{n}}, \quad (2)$$

where CV_j is the individual coefficient of variation for sample j and n is the number of samples. The analysis of the trabecular parameters was highly reproducible, except for EN. The RMS CV% was 1.14%, 0.35%, 3.52%, and 13.90% for TBA, HI, TMO, and EN, respectively.

4.2.4 Mechanical testing (III, IV)

The femora were tested in a side impact configuration, simulating a sideways fall on the greater trochanter (Fig. 7) (Eckstein *et al.* 2004). The femoral head and shaft faced downwards and were able to move independently of one another on the support plates during loading of the trochanter. One half of a tennis ball with a lubricant was used to simulate cartilage contact with the femoral head. The load

was applied to the greater trochanter through a pad, simulating a soft tissue cover. The shaft was positioned at 10° from horizontal, and the neck at 15° internal rotation. This standard position was used across all specimens. Loads were applied at a rate of 6.6 mm/s. The failure load was defined as the peak of the load-deformation curve. The test has been shown to display good reproducibility in previous tests on paired femora, the upper limit of the precision error being about 15% (Eckstein *et al.* 2004).

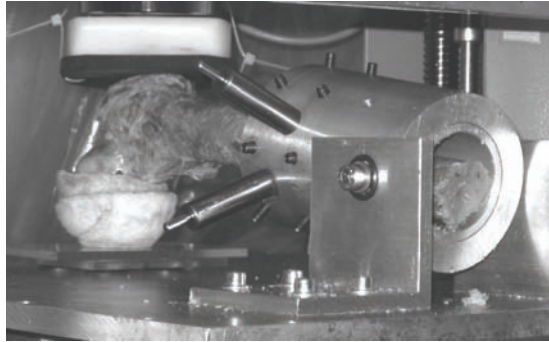


Fig. 7. The femora were mechanically tested in a side impact configuration, simulating a sideways fall on the greater trochanter.

4.3 Fracture classification

Fracture patterns were classified as being cervical (intracapsular) or trochanteric (extracapsular) according to the standard AO classification, generated by the AO foundation (Arbeitsgemeinschaft für Osteosynthesefragen). The same classification system was used both in the clinical and the experimental study series. Subcapital and transcervical (basicervical and midcervical) fractures were classified as cervical fractures, and pertrochanteric, intertrochanteric and subtrochanteric fractures as trochanteric fractures.

4.4 Statistical methods

The data were analyzed using the SPSS statistical software for Windows (SPSS Inc., Chicago, IL, USA, versions 11.5.1, 12.0.1, or 16.0). In all tests, $p < 0.05$ was considered to be statistically significant.

At first, the normality in the distribution of outcome variables was tested in all studies using the Kolmogorov-Smirnov test with the correction of Lilliefors. In order to detect the differences between study groups, a statistical evaluation for the normally distributed variables was performed with the independent samples Student's t-test or the Mann-Whitney's U-test for non-normally distributed variables. Levene's test was used to test the equality of variance in all analyses.

The correlations between outcome variables were primarily calculated using Pearson's linear correlation coefficients. On the contrary, Spearman's correlation coefficients were used in the non-normally distributed cases.

A stepwise multiple linear regression analysis (in studies I and IV) or logistic regression analysis with a forward stepwise method (in study II) was performed to identify the explanatory variables for a fracture. In study I, the sensitivity and specificity of the models were tested by calculating the area under the receiver operating characteristic curve (ROC). Statistical comparison between the areas under the ROC curves was also performed (Hanley & McNeil 1983).

In study III, χ^2 -test was used to test the overall difference in the proportion of fracture types between genders. Here, the sample was then divided into failure load quartiles of females and males for investigating the fracture type distribution at different levels of structural mechanical strength. The difference in the distribution of fracture types across the failure load quartiles was studied by the Kruskal-Wallis test. In this study, the gender and bone strength interaction with geometric variables was studied with ANCOVA, using gender and load quartiles as factors and age and total BMD as covariates. Similarly, the fracture type and bone strength interaction with geometric variables was clarified by using fracture type and load quartiles as factors and age and total BMD as covariates. Tukey's Post Hoc –test was used for the comparison of differences between quartiles.

5 Results

5.1 BMD and bone geometry in the clinical fracture risk assessment (I, II)

Correlation coefficients between BMD and geometrical parameters as well as descriptive data of the study populations divided by fracture types, and corresponding statistical comparisons between fractured subjects and controls are presented in the original papers.

5.1.1 DXA in discriminating fracture cases from controls (II)

The ability of DXA to discriminate fracture cases and controls to osteoporotic or non-osteoporotic group appeared to depend on the reference database. The best classification was obtained using the reference values of GE Lunar software version 7 and later for the calculation of T-scores (Table 10). Here, 19 cervical fracture cases out of 39 (48.7%) were classified not to have osteoporosis, when the lower of the femoral neck or trochanteric BMD T-score was used as a criterion of disease. More importantly, only one trochanteric fracture out of 18 (5.6%) was classified not to have osteoporosis. Even if the number of control subjects classified as having osteoporosis (5 out of 40) was higher compared with the other calculation references, the proportion of them compared with all controls was however relatively low (12.5%).

Table 10. The classification of different fracture types and controls to the osteoporotic or non-osteoporotic groups based on the lower of the femoral neck or trochanteric BMD T-score, calculated using different reference databases.

	GE Lunar Software before version 7		GE Lunar software version 7 and later		NHANES III recalculated	
	OP	Without OP	OP	Without OP	OP	Without OP
Cervical fracture	14 (35.9%)	25 (64.1%)	20 (51.3%)	19 (48.7%)	16 (41.0%)	23 (59.0%)
Trochanteric fracture	12 (66.7%)	6 (33.3%)	17 (94.4%)	1 (5.6%)	14 (77.8%)	4 (22.2%)
Any fracture	26 (45.6%)	31 (54.4%)	37 (64.9%)	20 (35.1%)	30 (52.6%)	27 (47.4%)
Controls	0 (0.0%)	40 (100%)	5 (12.5%)	35 (87.5%)	1 (2.5%)	39 (97.5%)

OP, osteoporosis

5.1.2 Combination of BMD and bone geometry (I)

The best explanatory variables for the different hip fractures are shown in Table 2 in the original paper I. For cervical fractures, the best combination was NSA, CFC, TRBMD, and WABMD. The area under ROC was 0.95 for this model, while the area under ROC for FEBMD or TRBMD alone was 0.74 (Fig. 8), which difference was statistically significant ($p < 0.001$). At a specificity of 80%, sensitivity was improved from 47.5% to 92.6% by the model compared to FEBMD or TRBMD alone.

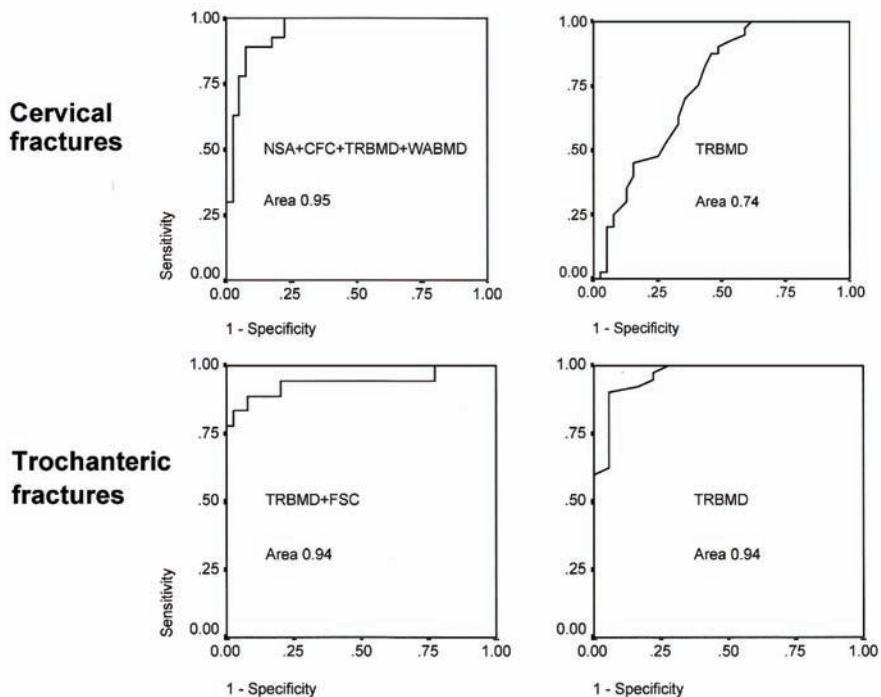


Fig. 8. ROC curves for the regression models (left) and for BMD alone (right).

The best explanatory variables for trochanteric fractures were TRBMD and FSC. The area under ROC was 0.94 for both the model and TRBMD alone (Fig. 8). A slightly higher value of 0.97 was achieved with FEBMD alone, which difference, however, was not significant. At a specificity of 80%, sensitivity was 94.4% with the model and with TRBMD alone.

5.1.3 Prediction of fractures in subjects without osteoporosis (II)

Since both the absolute TRBMD (I) as well as the lowest BMD T-score (II) were able to discriminate trochanteric fractures, additional analyses were not needed in these cases. Instead, the ability of BMD to predict cervical fracture was limited (I) and the number of cervical fractures appeared to be relatively high in the patients without osteoporosis as defined by BMD T-score threshold of -2.5 (II). Both results indicate that cervical fractures may be more effectively affected by other factors than BMD. Thus, we performed further analysis to elucidate if other measured parameters can offer additional information about the cervical fracture risk in these subjects without osteoporosis.

The differences in the measured parameters between the cervical fracture cases and controls in the subjects classified not to have osteoporosis based on the T-scores calculated according to the reference values of GE Lunar software version 7 and later are shown in Table 11. The cortical thicknesses (FSC and FNC) and NSA differed significantly between the groups ($p = 0.004$, $p = 0.002$, and $p < 0.001$, respectively). The cortex was thicker in the control subjects, whereas NSA was wider in the fracture cases. On the other hand, femoral neck and trochanteric BMDs were similar between the groups ($p = 0.92$ and $p = 0.88$, respectively).

Table 11. Differences in the measured parameters between the cervical fractures and controls in subjects classified not to have osteoporosis based on the T-scores.

	Cervical (N = 19)	Controls (N = 35)	p-value
Age (years)	70.3 ± 8.2	73.2 ± 5.5	0.12
Length (cm)	159.7 ± 5.6	159.5 ± 6.0	0.87
Weight (kg)	67.8 ± 11.1	68.6 ± 8.9	0.80
BMI	26.6 ± 4.4	27.1 ± 4.0	0.70
HAL (mm)	107.3 ± 6.9	104.3 ± 6.6	0.13
FNAL (mm)	89.4 ± 4.2	90.0 ± 6.1	0.69
FSC (mm)	6.1 ± 1.3	7.2 ± 1.1	0.004
FNC (mm)	3.4 ± 0.8	4.2 ± 0.9	0.002
NSA (deg)	135.3 ± 6.6	128.0 ± 5.1	<0.001
FNBM (g/cm ²)	0.85 ± 0.14	0.85 ± 0.08	0.92
TRBM (g/cm ²)	0.80 ± 0.14	0.81 ± 0.10	0.88

The classification of cervical fractures and controls among individuals without osteoporosis according to the logistic regression model is shown in Table 12. The explanatory factors in the model were NSA and FNC [OR = 1.23 (95% CI 1.06 –

1.42), and OR = 0.43 (95% CI 0.18 – 1.02), respectively]. Overall, 83.3% of all individuals without osteoporosis (N = 54) were classified correctly based on the model including only these two geometrical measures ($p < 0.001$). Only three controls out of 35 (8.6%) were classified as a case of cervical fracture. 68.4% of cervical fracture cases were correctly classified, but six out of 19 fell fallaciously into the control group.

Table 12. The classification of cervical fractures and controls among individuals without osteoporosis according to the binary logistic regression model.

Observed	Predicted (number of subjects)		
	Cervical fracture	Control	Percentage correct
Cervical fracture	13	6	68.4
Control	3	32	91.4
Overall percentage			83.3

Femoral neck-shaft angle and femoral neck cortex thickness were included in the model.

5.2 Assessment of experimental failure load (III, IV)

The study subjects were divided into failure load quartiles in study III, since the association of geometrical factors and structural mechanical strength with the distribution of cervical vs. trochanteric fractures was elucidated. In study IV, the relationship between trabecular bone structure and failure load as well as the combined power of geometrical and architectural parameters in the assessment of experimental failure load was investigated using the load as the continuous variable.

5.2.1 Bone geometry vs. failure load (III)

The failure load quartiles for both females and males as well as for the entire study population, the differences in geometrical parameters between fracture types by gender as well as the values of statistical significance for the geometrical parameters between females and males by fracture types are given in the original paper III.

When comparing the geometric parameters between the load quartiles, CFC and FSC were significantly lower in the first load quartile when compared to the other quartiles in the cervical fracture cases of females ($p < 0.001-0.003$). In the trochanteric fractures of males, CFC was significantly lower in the first and

second quartiles when compared to the highest quartile ($p < 0.01$). However, these differences disappeared after adjusting for age and total BMD. No other gender, fracture type or failure load quartile interactions with geometrical parameters were observed.

When looking at the differences in geometrical parameters between cervical and trochanteric fractures within the gender-specific failure load quartiles, there were no significant differences due to the limited sample size in the subgroups of female and male quartiles. Since there was no gender-specific difference in NSA, females and males were pooled together for a more detailed analysis of NSA within failure load quartiles. The NSA was higher in the cervical fracture cases in all failure load quartiles ($p < 0.01$ – 0.05) except in the quartile of lowest failure load, where the difference did not reach statistical significance ($p = 0.07$) due to the small number of specimens ($n = 7$) in the trochanteric group. The NSA did not differ between load quartiles within each fracture type.

The fracture type was significantly related to NSA ($r = 0.393$, $p < 0.001$ in females and $r = 0.293$, $p = 0.02$ in males). In females, fracture type correlated also with FNALb ($r = 0.308$, $p = 0.007$). However, neither NSA nor FNAL were related to failure load directly.

5.2.2 Trabecular bone structure vs. failure load (IV)

Significant relationships were found between the structural parameters of the trabecular bone and both BMD and failure load (see Table 1 in the original paper IV). The strongest correlations were found at the site-specific analyses within each fracture type.

In the cases of cervical fractures, the correlation coefficients of TBA, EN and HI, measured from the femoral neck or head area, with failure load were $r = 0.77$, -0.60 , and -0.68 , respectively ($p < 0.01$). For the trochanteric fracture cases, the corresponding site-specific correlation coefficients were $r = 0.73$, -0.70 , and -0.71 , respectively ($p < 0.01$).

5.2.3 Combination of bone geometry and trabecular bone structure vs. failure load (IV)

When combining the structural parameters of the trabecular bone and bone geometry using regression analysis, the highest coefficient of determination (R^2) values were obtained from the femoral head (ROI 3) for cervical, and from the

greater trochanteric area (ROI 4) for the trochanteric fracture cases. Thus, only the results of those sites are reported.

The best independent explanatory variables for the site-specific femoral neck BMD were TBA and cortical thickness (CFC) in the cervical fracture cases. These parameters explained 68% of the variation in DXA-based femoral neck BMD ($p < 0.001$). In the trochanteric fracture cases, HI and cortical thickness (FSC) explained as much as 87% of the variation in the site-specific BMD ($p < 0.001$) (see Fig. 4 in the original paper IV).

More importantly, failure load was also explained with a combination of trabecular and geometrical analysis. The standardized regression coefficients showed that most of the trabecular and geometrical parameters significantly contributed to proximal femur fragility (Table 2 in the original paper IV). However, the parameters were strongly intercorrelated causing consequently a multicollinearity problem, i.e. much of the variance in the dependent variable explained by one variable was also explained by other variable(s). Thus, multiple regression analysis was used to find the independent explanatory variables.

TBA and femoral neck axis length (FNAL) were the best independent explanatory variables for the failure loads in the cervical fracture cases. R^2 -value for the regression model was 0.64 ($p < 0.001$), which was the same for BMD (Fig. 9). When the trabecular and geometrical parameters were combined with the site-specific BMD in the cervical fracture cases, the best explanatory variables were femoral neck BMD and FNAL with the R^2 -value of 0.75 ($p < 0.001$). In the trochanteric fractures, EN and CFC were the best explanatory variables for the failure load ($R^2 = 0.66$, $p = 0.001$), while the site-specific BMD explained 72% of the variation in failure load ($p < 0.001$) (Fig. 9). None of the trabecular or geometrical parameters was independent of BMD in the combined model of geometrical and trabecular parameters and site-specific BMD in the cases of trochanteric fractures.

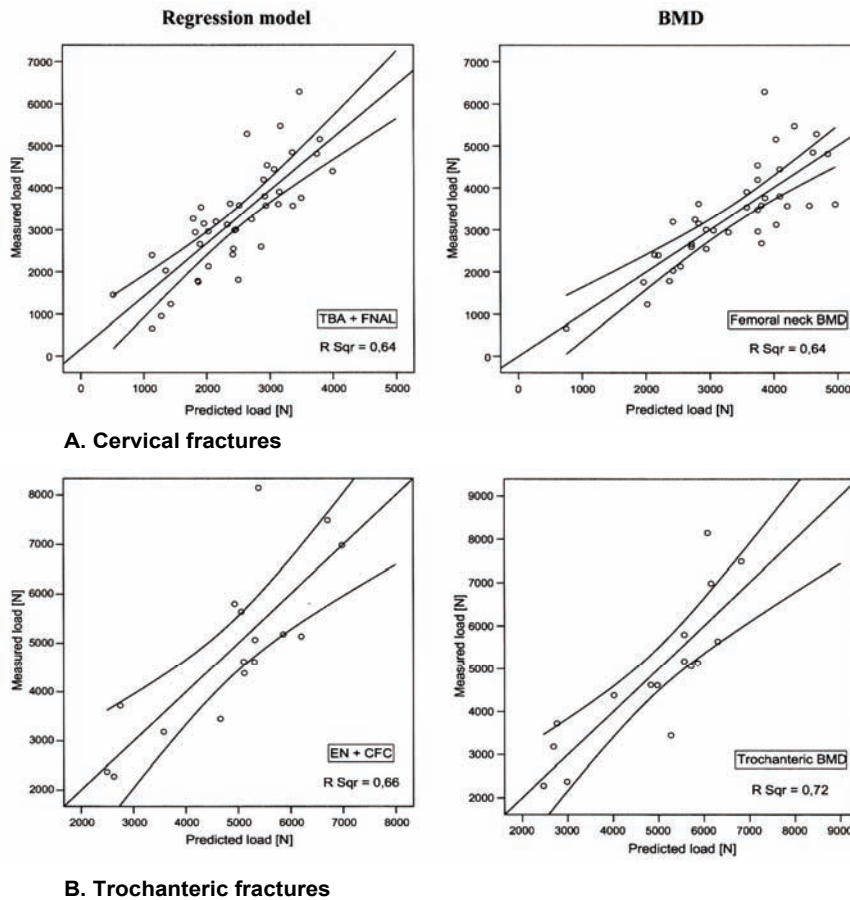


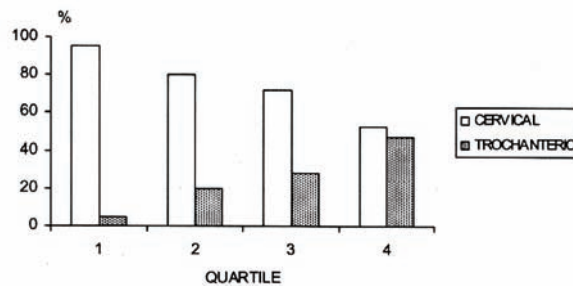
Fig. 9. Predicted vs. measured loads in the cervical and trochanteric fracture cases by the linear regression model and by site-specific BMD. The 95% confidence intervals are also indicated.

5.3 Biomechanical differences between hip fracture types (I–IV)

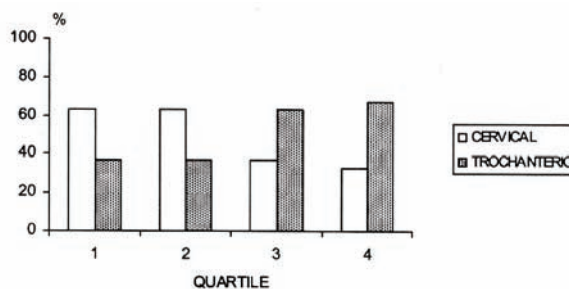
Clinical studies (I, II) showed that there are substantial differences in the explanatory factors between cervical and trochanteric hip fracture types. The experimental studies (III, IV) also supported this finding. In females, the NSA was significantly higher ($p = 0.001$) and the FNAL significantly longer ($p = 0.004$) in the cervical fracture cases, whereas in males only the NSA differed significantly ($p = 0.02$) between the fracture types. These differences also

remained after adjustment for age and total BMD. Furthermore, the explanatory factors differed between fracture types in the experimental study using a combined analysis of trabecular bone structure and bone geometry.

To further clarify the biomechanical behaviour of different hip fracture types, we experimentally explored the association of failure load level with the occurrence of cervical vs. trochanteric hip fractures. The overall proportion of cervical fractures was higher in females (74%) than in males (49%) ($p = 0.002$). The fracture type distribution differed significantly across the load quartiles in females ($p = 0.025$), but not in males ($p = 0.205$) (Figs. 10A and B). However, a similar trend was also found in men, with neck fractures predominating at lower load levels and trochanteric fractures at higher load levels. At the lowest load quartiles, 94.7% of fractures in female and 62.5% in male were femoral neck fractures whereas at the highest quartile only 52.6% of fractures in females and 33.3% in males were femoral neck fractures.



A. Females



B. Males

Fig. 10. The distribution of fracture types in the different failure load quartiles. (A) Females (N = 77). (B) Males (N = 63). For quartiles, see Table 1 in the original paper III.

6 Discussion

6.1 BMD and bone geometry in the assessment of cervical and trochanteric hip fracture risk

The present study indicated that the large variation in the mechanical competence of bone is associated with the geometrical variation of bone. The combination of BMD and bone geometry showed a significant improvement in the clinical assessment of the hip fracture risk compared with BMD measurements alone. Moreover, even though geometrical risk factors have also previously been shown to improve the discrimination of fracture cases (Alonso *et al.* 2000, Partanen *et al.* 2001, Gnudi *et al.* 2002, Gnudi *et al.* 2004), no previous evidence has demonstrated their competence within non-osteoporotic subjects – within those subjects that are not diagnosed using the current clinical procedure.

The clinical model of cervical fracture included the combination of NSA, CFC, TRBMD, and WABMD as the best explanatory variables. This combination was more sensitive and specific than BMD alone. The model underlines the importance of NSA and cortical thickness in the assessment of cervical fracture risk. The experimental results of the present study also highlighted the NSA as a significant discriminator between cervical and trochanteric fractures, with the NSA being substantially higher in cervical fractures. This was evident for all loading levels, for both genders and also before and after adjustment for age and BMD.

Interestingly, the NSA was not however found to differ between the low and high failure load fractures within each fracture type, which suggests that it is not a good predictor of failure load by itself. In general, clinical results concerning the importance of NSA in predicting fracture risk have been conflicting; whereas some studies did not find a significant impact (Karlsson *et al.* 1996, Center *et al.* 1998), others found an important relationship between NSA and fracture risk (Alonso *et al.* 2000, Partanen *et al.* 2001, Gnudi *et al.* 2002, Gnudi *et al.* 2004). In an experimental study of Kukla *et al.* (2002), authors reported that NSA showed a slight positive correlation with load-to-failure with the loading direction parallel to the shaft (vertical loading of the femur). In contrast, no significant correlation was reported between mechanical strength and NSA in the experimental study of Cheng *et al.* (1997b) with the mechanical test simulating a fall on the greater trochanter. In a cross-sectional clinical study, Alonso *et al.* (2000) reported that an

increase of 1 SD in NSA was associated with an odds ratio of hip fracture of 2.45 in men and 3.48 in women but they did not report any difference in NSA between the fracture types. Gnudi *et al.* (2002) have reported, in good accordance with our study, that NSA was a better predictor of femoral neck fractures than BMD. These findings might be explained by the high bending moment at the neck during a fall on the greater trochanter in femora with high NSA. Based on the current experimental results, it appears that NSA is the best discriminator for the fracture type albeit NSA is not associated with the magnitude of failure load in a side impact load configuration. Theoretically, the rotation angle of a leg at the moment of the floor contact may actually have a profound influence on the type of the hip fracture. This aspect is supported by the finding of Nevitt *et al.* (1993), where the nature of fall determines the type of fracture. In a falling situation, the rotation angle of a leg might compensate the effect of high NSA and a trochanteric fracture occurs. Anyway, the findings suggest that NSA may be used as a clinical tool for identifying subjects specifically with increased risk of cervical hip fracture.

The second explanatory factor in the clinical model of cervical fractures was cortical thickness. Similarly, the difference in the cortical thickness was also observed between genders and between load levels in the experimental study, the cortex being thinner in female and at the lowest load levels. However, the differences disappeared after adjustment for age and BMD. This indicates that cortical thickness is not independent of BMD and supports the previous findings, where it has been shown that cortical thickness correlates with DXA-based bone density (Rico *et al.* 1994, Szulc *et al.* 2006), i.e. they convey the same message. BMD measurement by DXA, which is a projectional method, is influenced by the thickness of the cortical shell, i.e. the thicker the cortex, the higher the values for DXA-based BMD.

The best explanatory combination for trochanteric fractures was TRBMD and FSC. However, FSC did not improve significantly the model of trochanteric fractures. The area under ROC was 0.94 both with and without FSC, which shows site-matched BMD to be the most important predictor of trochanteric fractures. The finding is also supported by other studies (Greenspan *et al.* 1994, Schott *et al.* 1998, Szulc *et al.* 2006), including an impressive population-based cohort study with 7598 white females, where trochanteric BMD was a stronger predictor of intertrochanteric (RR = 4.5) than cervical fractures (RR = 1.8) (Schott *et al.* 1998).

The importance of bone geometrical measures for the prediction of fracture risk in patients without osteoporosis is also supported by the current study.

Although the majority of fractures occur in individuals diagnosed as non-osteoporotic (Stone *et al.* 2003, Schuit *et al.* 2004), there is a lack of information regarding factors predisposing to hip fracture in these patients. The present study clearly confirmed that the risk of trochanteric fracture can be predicted based on BMD measurements, whereas only geometrical risk factors were able to discriminate cervical fracture cases among those individuals classified not to have osteoporosis. Only one trochanteric fracture patient out of 18 was classified as non-osteoporotic when the lowest BMD T-score value was used. On the contrary, the capability of the BMD T-score to predict a cervical fracture was limited to the individuals with low BMDs. The results clearly suggest that the presence of a DXA-based T-score higher than -2.5 alone is not a sufficient argument for the clinical decision not to treat. A high DXA-based BMD would seem to eliminate the need for intervention/treatment in cases associated with an increased risk of trochanteric, but not cervical fracture. Therefore, it can be argued that individuals with BMD in the non-osteoporotic range may still be at the risk for cervical fracture.

In these patients without osteoporosis (as defined by DXA-based BMD T-score), we observed significant differences in bone geometry between the cervical fracture cases and controls. Our results are in good accordance with the previous prospective study of Robbins *et al.* (2005), in which multiple factors appeared to be more strongly associated with hip fractures in women with high BMD compared to those with low BMD. It seems thus to be evident that attention should also be focused on individuals with high BMD in fracture risk assessment. Even though the fracture type was not classified in the study by Robbins *et al.* (2005), “the finding of factors associated with hip fracture in those with high but not low BMD is consistent with the generally accepted concept that BMD alone explains less than half of the risk of hip fracture”. Based on our present study with hip fracture type classification, the fractures that BMD is not able to explain most likely occur at the femoral neck. This indicates that cervical fractures are significantly affected by factors other than BMD.

In the present study, 83.3% of individuals without osteoporosis were correctly classified as cervical fracture cases or controls based on only two geometrical parameters in the model. Here again, neck-shaft angle and femoral neck cortex thickness were the best explanatory factors for cervical fracture. The result confirms that the widening of the NSA increases the risk of cervical fracture (Alonso *et al.* 2000, Partanen *et al.* 2001, Gnudi *et al.* 2002, Gnudi *et al.* 2004). Even if cervical fractures are associated with the NSA, and the low failure load

fractures are typically cervical, the use of NSA in the prediction of cervical fractures remains still unclear since the experimental data showed no direct correlation between NSA and failure load.

The second explanatory variable in the regression model for the individuals without osteoporosis was cortical thickness. FNC is a protective factor against the cervical fracture (OR = 0.43), i.e. the thickening of cortex reduces the risk of cervical fracture. Even though our first clinical study, together with previous studies, indicated that cortical thickness correlates with DXA-based bone density (i.e., that both measures convey the same message) (Rico *et al.* 1994, Szulc *et al.* 2006), the result provides further clarification on the issue by indicating that cortical thickness can yield independent information beyond BMD. It has a discriminative capability in the cases without osteoporosis as well, where the ability of BMD to discriminate fractures from controls is negligible.

Altogether, these findings indicate that geometrical parameters can offer additional information for the assessment of cervical fracture risk in individuals without osteoporosis – in those patients who cannot be identified to be at high risk of fracture according to the current diagnostic method. However, it is important to remark that the proportion of false negatives (31.6%) was still relatively high in the regression model for the individuals without osteoporosis. This indicates that bone geometry alone is not absolutely adequate. Additional predictors, such as structural factors of the trabecular bone, are thus also needed for more exact fracture risk estimates, as the current comprehensive strategy for the assessment of fracture risk also suggests (Kanis 2002, Järvinen *et al.* 2005, Hernandez & Keaveny 2006).

6.2 Bone geometry and trabecular bone structure in the assessment of experimental failure load

In the present study, we tested the hypothesis that the structural parameters of trabecular bone together with geometrical parameters of the proximal femur, as obtained from radiographs, are able to predict experimentally determined failure loads. To our knowledge, no previous study has examined this relationship *in vitro* by experimentally determining failure loads. However, radiographic techniques are widely available throughout the world, and they may be suitable to use for the determination of both bone trabecular structure and geometry. Thus, it would be beneficial if fracture risk could be estimated from these, in particular in areas where DXA is not widely available.

At first, the results showed that the measured structural parameters were significantly associated with DXA-based BMD, in particular, when the geometric factors and the trabecular bone structure were combined. In the cervical fracture cases, 68% of the variation in the femoral neck BMD, and in the trochanteric fracture cases, up to 87% of the variation in the site-specific BMD, could be predicted. This result indicates that a substantial part of the variability in DXA-based BMD can be estimated from plain radiographs, if appropriate algorithms are applied. Several authors have reported, in good line with the present experimental study, the successful identification of osteoporotic patients from controls, using texture analysis of trabecular bone derived from radiographs (Pothuau *et al.* 1998, Benhamou *et al.* 2001, Gregory *et al.* 2004, Chappard *et al.* 2005, Vokes *et al.* 2006), suggesting the potential role of conventional roentgenography for the evaluation of fracture risk.

More importantly, we found that a combination of structural and geometric parameters was particularly powerful in predicting the mechanical failure loads of the femur. The coefficient of determination was similar to that obtained for DXA-based BMD. The trabecular bone area, one of the predictive variables for cervical fracture in the model, was shown to correlate with DXA-based BMD. The second explanatory variable, FNAL, has been shown to be an independent predictor of cervical fracture risk (Duboeuf *et al.* 1997, Bergot *et al.* 2002, Gnudi *et al.* 2002, Gnudi *et al.* 2004), although findings in the literature are not uniform (Karlsson *et al.* 1996, Center *et al.* 1998, Alonso *et al.* 2000, Partanen *et al.* 2001). Indeed, the significant difference in FNAL was not observed between cervical or trochanteric fracture cases and controls in the present clinical study. Here again, this controversy between results may be explained by the standardized testing protocol in the experimental study design, mimicking the sideways fall on the greater trochanter. Mechanically considering, FNAL, however, is a potential risk factor for the femoral neck fracture, i.e. the longer the FNAL, the higher the bending moment in the neck, as it has also been suggested previously (Yoshikawa *et al.* 1994, Szulc *et al.* 2006).

In the trochanteric fracture cases, Euler's number and cortical thickness were the best explanatory variables of failure loads. Euler's number, as a measure of connectivity, has also previously been shown to be a predictive parameter of mechanical strength that is independent of bone mass or density (Portero *et al.* 2005). Cortical thickness, the second explanatory variable in the model, has also been previously shown to predict mechanical competence of bone in experimental (Augat *et al.* 1996) and clinical studies (Gnudi *et al.* 2002, Szulc *et al.* 2006), as

also presented above. It has been proposed that there is more irregular and anisotropic structure in the trochanteric region compared with a much more constant and isotropic structure of the femoral head (Krug *et al.* 2005), which might explain why a structure-related parameter (EN) is part of the model, explaining trochanteric but not cervical fractures. This provides further support for the concept that the specific risk factors of cervical and trochanteric fractures differ (Mautalen *et al.* 1996, Duboeuf *et al.* 1997, Fox *et al.* 2000, Partanen *et al.* 2001, Gnudi *et al.* 2002, Szulc *et al.* 2006) and fracture types should thus be evaluated separately.

In the present study, the explanatory power for bone mechanical strength was higher than reported previously (Lin *et al.* 1999), even when using novel imaging modalities (Link *et al.* 1998, Hudelmaier *et al.* 2005, Krug *et al.* 2005, Lammentausta *et al.* 2006). However, none of the earlier studies investigated the combination of geometrical and trabecular analysis for the assessment of failure load. This is an important aspect in the skeletal sites, where both the cortical and the trabecular bone are present (Järvinen *et al.* 2005), such as in the proximal femur. In vertebral bone, the predictive power of texture parameters for strength, as defined from radiographs, was $R^2 = 0.64$ in females (Veenland *et al.* 1997). Taking these findings and our data in conjunction, the results support the notion that the combination of bone geometry and trabecular structure is of particular importance in evaluating the strength of the proximal femur, while the contribution of trabecular bone to vertebral strength is dominant.

Chappard *et al.* (2005) have concluded that fracture risk evaluation can further be improved by adding information related to the directional organization of trabecular bone. However, we did not find correlations between trabecular main orientation and failure loads. The contribution of trabecular orientation on the fracture risk is not totally clarified, but the conflict in results may be due to the differences in methodology. The importance of trabecular orientation may further be elucidated with the method proposed by Stauber and Müller (2006), where the local morphometric analysis on element level (i.e. analysis of single trabecular rod and plate elements) is performed. On the other hand, the presence or absence of the certain oriented trabeculae might have a stronger influence on fracture risk than the orientation angle of individual trabecular rod or entire trabecular pattern. Chappard *et al.* (2005) have speculated that osteoporosis is characterized by a preferential loss of trabeculae having less mechanical competence. This perspective is also supported by the study of Wigderowitz *et al.* (1997) with radiographs at the distal radius, where the authors observed a

preferential orthogonal 2-D structure in fractured patients and explained the finding by the absorption of transverse trabeculae. Thus, the increased anisotropy caused by the resorption of certain oriented trabecular structure might contribute to the fragility of bone more than the absolute value of the orientation angle.

A similar effect might explain the site-specific differences in the correlation between the trabecular parameters and BMD or failure load. The degree of anisotropy depends on the skeletal sites (Link *et al.* 1998, Chappard *et al.* 2005, Krug *et al.* 2005). Here, the femoral head seemed to be the most sensitive for trabecular resorption in the cases of cervical fracture, and the trabeculae of the greater trochanteric group in the cases of trochanteric fracture. These findings clearly emphasize the importance of standardization of measurements, especially for the determination of ROI. However, the analysis of femoral head is not directly transferable to a clinical radiograph, since the clinical hip image includes the acetabulum in addition to the femoral head, which structures are projected one upon the other.

The methodology used in this study needs to be discussed. We applied the local gradients of image instead of absolute gray level values or fractals that have been utilized previously (Pothuaud *et al.* 1998, Lin *et al.* 1999, Chappard *et al.* 2001, Benhamou *et al.* 2001, Veenland *et al.* 2002, Chappard *et al.* 2005, Guggenbuhl *et al.* 2006). We were thus able to avoid the thresholding of the images, the method being insensitive to the intensity or contrast variations caused by the image acquisition conditions. Even if there were differences in these conditions in the roentgenography set-up, causing consequently variations in the image quality, the method was highly applicable for the segmentation and quantification of the trabecular pattern. Veenland *et al.* (2002) have concluded, in good accordance with us, that the features of the morphological gradient method are inherently independent of linear gray-scale transformations.

However, the current study has limitations that need to be mentioned: 1) Fracture strength was evaluated experimentally, and these results need to be confirmed in clinical studies before they can be applied in clinical patient management; 2) The specimens were fixed in formalin, which might have some effect on the mechanical properties. Anyway, all the samples were handled similarly, and the relatively high correlations found here might have been even more pronounced if fresh samples had been used. We therefore assume that fixation does not affect the conclusions drawn from this study; 3) Measurements of bone structure were obtained in 2D and not in 3D; however, previous studies have shown that 2D results correlate well with 3D data measured by

microcomputed tomography (Guggenbuhl *et al.* 2006) and with the direct analysis of bone microstructure by histomorphometric technique (Chappard *et al.* 2005); 4) The radiographic method used here was intended for experimental studies, which only partially reflects the typical clinical X-ray examination conditions. However, the method resulted in radiographs with a variety of contrast and overall radiographic quality, typical also in clinical X-rays. The presented image processing method appeared to be able to recognize the structure relevantly, indicating that it might be applicable for clinical setup as well; 5) Radiographs were obtained *ex vivo* without the presence of soft tissues, and thus, the correlation may be somewhat higher than for *in vivo* conditions. However, the same was true for the DXA measurements, which were taken *ex vivo*, and these have been shown to be substantially affected by the presence of soft tissues (Lochmüller *et al.* 2001). Since our methodology does not rely on the absolute X-ray absorption, which may be impacted by soft tissues, but on the structural information in the radiograph, we assume that the soft tissue errors of DXA will be stronger than those of the radiographic measurements, so the current study more likely overestimated the potential of DXA to predict fracture strength than that of radiography. It can thus be argued that the methodology is favour to be further developed for clinical purposes, since it seems to have potential in applying it for the screening of risk subjects. The gradient-based image analysis should also be independent of the imaging modality used, which theoretically would provide the direct estimate for individual fracture risk in terms of bone strength.

6.3 Biomechanical differences between hip fracture types

Despite the general consensus on the multifactorial background of hip fracture, covering “the sum total of characteristics of the bone that influence the bone’s resistance to fracture”, as the National Institutes of Health conference has defined bone quality (Fyhrie 2005), less attention has been paid to the fact that the predictive factors for different hip fracture types (intracapsular and extracapsular, i.e. femoral neck and trochanteric fractures) differ significantly (Mautalen *et al.* 1996, Duboeuf *et al.* 1997, Fox *et al.* 2000, Partanen *et al.* 2001, Gnudi *et al.* 2002, Szulc *et al.* 2006). Consequently, the mechanical behaviour of different types of hip fractures can rationally be considered to be different. Since the assessment of fracture risk should encompass all aspects of risk (Kanis 2002, Sambrook & Cooper 2006, Cheung & Detsky 2008), it can be argued that the

same scheme should be adopted for the risk assessment of different types of hip fractures – by taking also into account the multifactorial background of different hip fracture types, i.e. different pathophysiological mechanisms between different types of hip fractures.

The perspective to take the fracture type into account in the fracture risk assessment is also strongly supported by the present experimental study, where it was analyzed, for the first time, the association of different levels of structural mechanical strength and geometric factors with the occurrence of cervical vs. trochanteric hip fractures in a controlled experimental setup. The study shows that, in an experimental setup, hip fractures in femora with low mechanical strength predominantly occur at the femoral neck, in particular in females, whereas trochanteric fractures appear to be more common in femora with higher failure loads. This suggests that the strength properties of the femoral neck dominate at loads lower than the breaking force of the trochanter, i.e. femora with low bone strength are particularly vulnerable at the level of the femoral neck, whereas those with higher bone strength preferably fail at the trochanter.

Considering that bone strength (failure load level) is likely to decrease with age, this appears to be somewhat controversial to epidemiological findings, where trochanteric fractures have been shown to be progressively more common with increasing age (Kannus *et al.* 1996, Lofman *et al.* 2002). This controversy might be explained by the standardized testing configuration, mimicking a sideways fall on the greater trochanter, using a fixed low loading rate. Numerous comprehensive studies on risk factors of fractures among elderly people have shown that falling is the strongest single risk factor for a fracture and the type and severity of falling are crucial in determining whether or not a fracture occurs (Hayes *et al.* 1993, Dargent-Molina *et al.* 1996, Wei *et al.* 2001, Robinovitch *et al.* 2003, Kaptoge *et al.* 2005). Furthermore, it was already shown in 1996 by Pinilla *et al.* that the impact direction associated primarily with the fall is a critical determinant of hip fracture risk that is both independent of bone density and associated with fall biomechanics (Pinilla *et al.* 1996). Using an analysis of covariance to adjust for total hip BMD, they showed that failure load decreased by 24 % as the loading angle changed from 0 degree to 30 degrees, which reduction in failure load is comparable to that associated with about 25 years of age-related bone loss after the age of 65. Instead of fall biomechanics, the present study gives information on the hip fracture mechanisms independent of the falling. It is indisputable that most fractures occur through a fall and that the falling mechanism plays a crucial role in determining whether or not a fracture occurs.

However, the type of falling as a strong determinant for the occurrence of a fracture may lack the structure related information behind the fracture mechanisms. In the experimental study design, the type of falling can be eliminated as the well-known factor for fracture susceptibility and the mechanisms behind the phenomena (fracture) can be further elucidated. Our finding might thus be clinically important, since it suggests focusing on the identification of risk factors associated with low mechanical strength. When this finding is combined with the outcome of the present clinical study with individuals without osteoporosis, the evaluation of bone geometry should further be emphasized especially in the assessment of cervical fracture risk. Considering an individual with BMD in normal range (without osteoporosis), the cervical fracture risk may still be increased as suggested by the present clinical study, since the mechanical strength of bone may be reduced as the experimental study points out. This clearly suggests that we should focus on the identification of risk factors associated with low mechanical strength – on the geometrical risk factors that predispose to cervical hip fracture.

6.4 Future aspects in fracture risk assessment

In this chapter, some concerns about the prevailing practices in the current fracture risk assessment are highlighted. Proposals for the improvement of individual fracture risk evaluation are also presented based on the results of this thesis.

6.4.1 Current conflicting concept of “osteoporotic fractures” – bias in the DXA-driven research

DXA-based BMD has been a benchmark in the assessment of fracture risk since the WHO established a new definition of osteoporosis (Anonymous 1993, Anonymous 1994). Even if researchers are currently well cognizant of the facts that a fracture is a multifactorial event and that the fracture risk can not be determined by only DXA-based BMD measurements, clinicians still rely on BMD for fracture risk assessment and treatment decisions (Cheung & Detsky 2008).

Due to the multifactorial etiology of fracture, reduced bone mass is only one single risk factor for fracture. Indeed, its ability to predict fracture is limited (Wilkin & Devendra 2001, Kanis 2002, Stone *et al.* 2003, Schuit *et al.* 2004).

Consequently, the widely used term “osteoporotic fracture” is questionable, at least partly, since the final reasons for the occurrence of fracture incident are not typically known. It should be kept in mind that over half of the “osteoporotic fractures” occur among people who can not be classified as having osteoporosis according to the current clinical practice (Stone *et al.* 2003, Schuit *et al.* 2004). The term “osteoporotic fracture” has thus a high level of abstraction, where the paradoxical dominant role of DXA can be seen. Indeed, “osteoporotic fracture” simply means a fracture caused by low-impact trauma, i.e. the fracture that is related to the reduced bone mechanical competence by one way or another, but not necessarily to osteoporosis as defined by BMD measurements with DXA.

The current conflicting concept of DXA-driven research can also be seen elsewhere. The deterioration of bone structure is associated with osteoporosis (Anonymous 1993). Even if this deterioration may naturally be the consequence of reduced bone mass, we do not have quantitative structural measure for it, since DXA is not able to characterize bone structure. In other words, the structural deterioration in osteoporosis can not be characterized based on the diagnostic BMD criteria. It is possible, and even probable that the measurable structural deteriorations happen prior to diagnosed osteoporosis, i.e. prior to the DXA measurement is able to detect them. The fact that the ability of BMD to predict fracture is limited gives us a very important clue to this issue.

“An engineer would laugh if asked to predict the strength of a very complex structure like the proximal femur, given only the information available to the clinician” (Currey 2001). Thus, the development of new methodology for fracture risk assessment should clearly be based on the current definition of osteoporosis, whereby explicit knowledge of the bone structure is needed. This requires relevant methodology for the detection of structural deterioration and quantitatively measurable clinical decision criteria. The excuse that we do not currently have a better method is not satisfactory. The present study shows that even a very conventional imaging alternative exists and may be appropriate to exploit in the clinical assessment of hip fracture risk in the future.

6.4.2 Concern about the prevailing practice in fracture risk assessment – fracture type should not be ignored

In addition to the need for changes in the DXA-driving research, we have evidence that clinical fracture risk assessment should be made separately for different types of hip fractures, as they are also classified for the diagnosis and

treatment of hip fractures (Parker & Johansen 2006). This suggestion, as such, is not unique. Mautalen *et al.* published a review as early as 1996 stating that the two main types of hip fractures should be evaluated separately in order to increase both the knowledge and the future likelihood of preventing hip fractures (Mautalen *et al.* 1996). However, more than ten years later the prevailing practice seems to be unchanged. Even the recent WHO fracture risk assessment tool that combines clinical risk factors with and without BMD (Kanis *et al.* 2008a) ignores not only some general risk factors (Cheung & Detsky 2008, Järvinen *et al.* 2008), but also characteristics of different fracture types. This thesis provides strong additional evidence that intracapsular hip fractures are substantially influenced by risk factors other than those of extracapsular ones and that low- and high-energy hip fractures have biomechanically different origins and result in anatomically different hip fracture types. Therefore, the concern can be expressed that the classification of hip fracture types has been ignored in the majority of recent studies.

To advance the prediction of fractures to the next level, further modifications in the current practices are obviously needed. In addition to the need to broaden the current fracture risk models to include both missed extra-skeletal risk factors and some vital bone-related parameters beside BMD (Cheung & Detsky 2008, Järvinen *et al.* 2008), decision criteria for both intracapsular and extracapsular fracture risk should be composed, and the risk score of the site most vulnerable to the fracture should be used when making the treatment decision.

In addition to fracture risk assessment, the perspective presented here might also pertain to fracture prevention. Currently, there are no studies where fracture prevention has been studied using the hip fracture type as a guideline. Intuitively, if one physical exercise has a positive impact in trochanteric and/or femoral neck BMD, another exercise with a different loading direction might amend the internal bone structure and/or bone geometry and, in consequence, further reduce the fracture risk. This perspective is supported by the study of Nikander *et al.* (2005), in which the femoral neck structure was evaluated in female athletes subjected to different loading modalities. The authors concluded that mechanical loading and its modality are strong external determinants of the structure and concomitant strength of the femoral neck (Nikander *et al.* 2005). The same might also pertain to medication and its ability to reduce the susceptibility of a trochanteric hip fracture by increasing trochanteric BMD, while its effect on the risk of an intracapsular fracture might be more limited. Therefore, it might be possible to substantially reduce future hip fractures if an adequate intervention

can be focused on the reduction of certain risk factors of a certain fracture type with a specific focus on the site where the absolute risk is the highest. This is a good ambition, but it cannot be achieved without fracture type classification.

7 Conclusions

The present study indicated that the large variation in the mechanical competence of bone and in hip fracture risk is associated with the geometrical and architectural variation of bone. Moreover, the study suggests that the etiopathology of different types of hip fractures significantly differs, and that fracture risk should thus be evaluated separately for cervical and trochanteric hip fractures. Based on the study, the current clinical procedure can better be used for the assessment of the risk of trochanteric fracture, whereas cervical fracture is more strongly affected by the geometrical factors than by BMD. Finally, the study showed that the radiograph-based structural parameters of trabecular bone and bone geometry predict in vitro failure loads of the proximal femur with quite similar accuracy as DXA when using appropriate image analysis technology. This suggests that the technology may be suitable for further development and application in clinical fracture risk assessment. Based on the aims of this study, it can specifically be concluded that:

1. The combination of BMD and bone geometry significantly improves the assessment of hip fracture risk compared with BMD measurements alone.
2. The risk of trochanteric fracture can be evaluated based on the BMD T-score, whereas the radiograph-based bone geometrical measurements can improve the assessment of the cervical hip fracture risk in subjects diagnosed not to have osteoporosis based on the current clinical procedure.
3. The incidence of different fracture types significantly differs in different experimental failure load levels. Femoral neck fractures predominate at the lowest structural mechanical strength levels, whereas trochanteric fractures are more common at high failure loads. The best predictor of fracture type across all structural strength levels and both sexes is the femoral neck-shaft angle.
4. The developed gradient-based image analysis method is suitable for the evaluation of trabecular bone structure. The combination of the radiograph-based geometrical and architectural structure of bone can be used for the assessment of experimental failure load with similar accuracy to DXA.

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