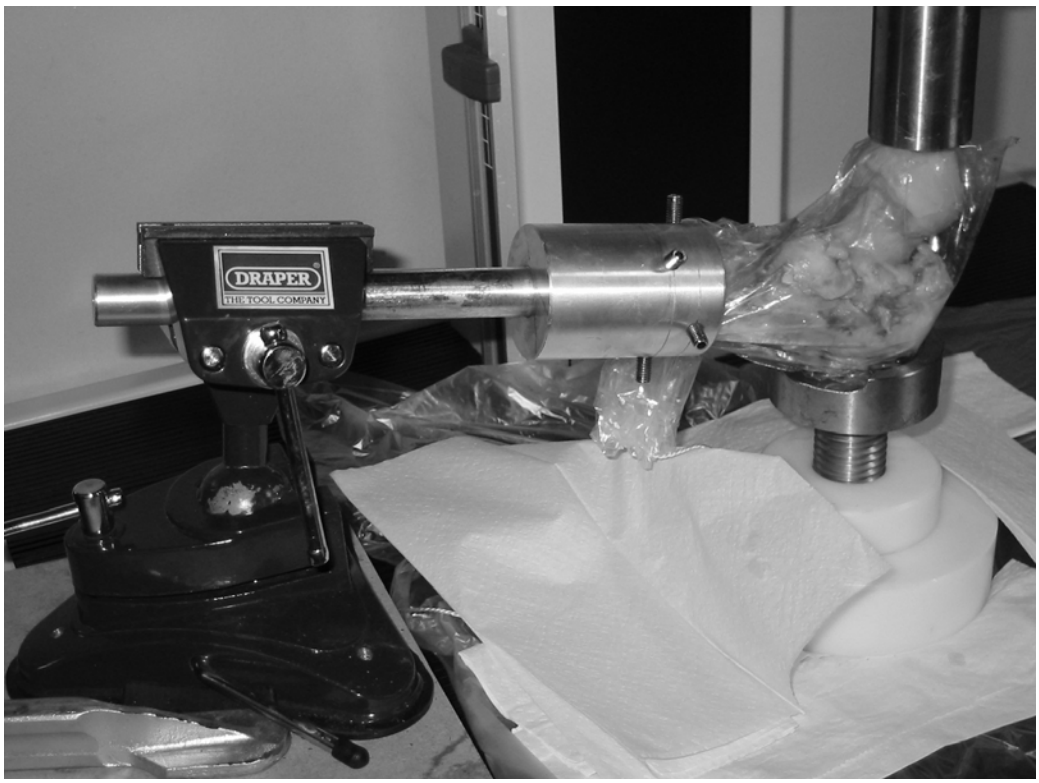
PhD Thesis



Hip geometry in relation to bone strength and risk of fracture in the proximal femur

Ph.D. Thesis
by
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Preface

The work presented in this thesis is based on studies carried out in the Department of Endocrinology, Odense University Hospital, the Osteoporosis Research Clinic, Hvidovre Hospital and Department of Endocrinology, Aarhus University Hospital in the period from December 2000 to late autumn 2007. Working on the thesis has been an exciting and inspirering task. At some points the work has been difficult and full of challenges. However, the long time span working with data has to some extend made it possible for me to explore and improve my results.

During the last 7 years I have had the privilege to work with a huge bunch of nice and friendly people. The relations with many of you will last in the years to come, and some of us will keep on doing research together – although I am heading towards being the surgeon with the saw and drilling-machine. It is characteristic for you all that you are very enthusiastic and flexible. You are all hungry for cooperation and you look at the possibilities rather than focusing at the problems. You are good friends, and have brilliant brains – and a good sens of humor. I am grateful to all of you – this thesis had not been possible without your help and cooperation. The space in this preface unfortunately is limited, therefore – thank you ALL by my heart.

However a few persons deserve a few lines. First I would like to thank, **Kim Brixen**, who made all my work possible. He introduced me to the world of research and understood me as the person I was at the time I started up working in his group on the department of endocrinology, Odense University Hospital. He is my mentor, and I am grateful to his supervision, perfectionism, his friendship, empathy, and understanding. Thank you.

I am also very pleased with the cooperation with my second supervisor, **Jens-Erik Beck Jensen**. He introduced me to a very interesting field of research; the strength analysis.

The never ending enthusiasm from Jens-Erik and his staff, the flexibility, the friendship, and the willingness to help with all sorts of things made this thesis possible. Many pleasant visits and days of work in Hvidovre gave this thesis its unique touch. Thank you.

Furthermore I am grateful to my third supervisor on the thesis, **Ellen Hauge**. She always responded quickly and gave good support and high quality of supervision. Ellen was the contact person to the Department of Forensic Medicine in Aarhus, and she introduced me to the nice, helpful, and friendly staff there.

I also want to thank and acknowledge the economical supporters listed below. They made my study possible.

Finally I want to thank my family for their interest and patience during the period of making the thesis. Especially my wife **Helle** is thanked for her support – I am deeply grateful for that. Furthermore my daughters **Freja** and **Lærke** are thanked for their patience and understanding in the periods when I was both physically and mentally in front of my laptop and not in front of them. They are the reason for why I got into research, and they are continuously reminding me of essential priorities in life. Doing research have been a quality and a good investment in me and my family's lives.

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List of abbreviations

BMD	**Bone Mineral Density**
BMD_{vol}	**Volume Bone Mineral Density**
BMI	**Body Mass Index**
CR	**Conventional radiographs**
CSMI	**Cross-sectional moment of inertia**
DXA	**Dual energy x-ray absorptiometry**
FNAL	**Femoral neck axis length**
FE	**Finite element analysis**
FX	**Fracture**
HAL	**Hip Axis Length**
HD	**Head diameter**
HF	**Hip fracture**
HR	**Head radius**
HSA	**Hip Strength Analysis**
LOD	**Logarithm of the odds**
NSA	**Neck Shaft Angle**
NW	**Neck width**
OP	**Osteoporosis**
PCR	**Polymerase Chain reaction**
PTH	**Parathyroid hormone**
SA	**Strength analysis**
SD	**Standard deviation**
SERM	**Selective estrogene reuptake modulators**
SI	**Singh Index**

Bone structure and hip geometry in relation to strength in the proximal femur

Table of contents:

1. List of publications

This Ph.D. thesis is based on the following papers:

I. **N. Nissen, E.M. Hauge, B. Abrahamsen, J-E Beck Jensen, L. Mosekilde, K. Brixen.** Geometry of the Proximal Femur in Relation to Age and Sex; A Cross-Sectional Study in Healthy Adult Danes. Acta Radiologica. 2005 Aug;46(5):514-8

II. **N. Nissen, J.S. Madsen, E.M. Bladbjerg, J-E Beck Jensen, N.R. Jørgensen, B. Langdahl, B. Abrahamsen, K. Brixen.** No association between hip geometry and four common polymorphisms associated with fracture – The Danish Osteoporosis Prevention Study. Submitted to Calc. Tiss. Int. CTI-08-0166

III. **N. Nissen, EM Hauge, A Vesterby, B Abrahamsen, K Brixen, J-E Bech Jensen.** Femoral neck axis length predicts bone strength in the proximal femur – A human autopsy study. Submitted to Bone D-08-00482

IV. **N. Nissen, J. Ryg, K. Brixen.** Femoral neck axis length is increased in patients with recent hip fracture. A case-control study. In preparation

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2. Introduction

In Denmark, approximately 10,000 patients suffer a hip fracture (HF) per year (1). The vast majority of these fractures occur in the elderly and the incidence increases steeply with age. HF in elderly patients are associated with a substantial mortality and morbidity (1-8). Thus, the mortality is increased with hazard ratio up to 6.28% in the first six months after the first HF (6) and a recent Danish database study (9) showed an excess mortality of 19.6 % the first year after HF. Although, the mortality (3;5) and morbidity (5;6;10) after HF to a large degree can be attributed to co-morbidity (3;5), the risk of sustaining a second HF is increased by a factor of 2.3 (11). The post-operative complications and ability to participate in rehabilitation also counts in the morbidity (12;13). Nevertheless, one year after a hip fracture 20 to 40% of the patients are unable to walk independently (14;15) and 60% have decreased activity of daily living score (5;16) 14% will require nursing home (3). Finally, HF imposes large economic burdens on the society (3;17). Similarly, the direct costs for the Danish society every year because of HF have been estimated to DKr 2.8 billion (18).

Although, only 1–5% of all falls in the elderly lead to a HF, approximately 90% of all HF are caused by a direct fall on the major trochanter (19;20) and fall-related factors such as the direction of the fall (21) decreased muscle mass, gait speed, agility in tandem walk, and visual acuity are significant risk factors for HF (22). In addition, age, previous history of fracture and low body weight or body mass index (3;4;6;9;10;23) increase the risk of HF (table 1).

Table 1: Risk factors for HF compiled from prospective studies (10;16;22;24).

- Age
- Osteoporosis
- Hereditability for osteoporosis
- Women with low body weight (BMI < 19 kg/m2)
- Previous low energy fracture
- Systemic glucocorticoid treatment
- Elderly with high risk of falling
- BMD

Finally, the risk of HF is closely associated with bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DXA) at the hip. Thus, a number of prospective and cross-control studies as well as and meta-analyses have demonstrated that the relative risk for hip fracture is 2.6 (2.0 to 3.5) for each standard deviation (SD) decrease in BMD of the hip (16;21;22;25;26). Indeed, the majority of patients with HF have osteoporosis (3;21;27-29). BMD at other anatomical sites, e.g. calcaneus, phalanges of the hand (30-32), and the lumbar spine (32) also predicts the risk of HF, however, less closely than BMD at the hip. Also, BMD as measured by CT-scans or MR-scans (33-36) predicts the risk of HF. Use of CT-scans is not possible for screening, however, because of the higher radiation dose compared to conventional X-rays (CR) and DXA. Finally, ultrasound measurements of the *i.e.* heel and ultradistal forearm (37-39) also predicts the risk of HF, however, such measurements, add little to the fracture prediction compared to DXA alone (40).

Post-mortem studies on human proximal femurs have shown that BMD measured by DXA explains approximately 80% of the variation in strength in the femoral

neck (38;41;42). Some observations, however, suggest that the predictive power of BMD is less than perfect. Thus, from the age of 60 to the age of 80 years the risk of sustaining a HF rises 13 times (43), but the decrease in BMD over these two decades of life can only explain a doubling in risk of HF. Also, the risk of HF increases with a factor of 3.7 for each decrease of one SD in BMD at age 50, but only a factor of 1.70 at age 90 (26). This may be due to the fact that DXA does not take the macro- and microscopic structure or the quality of the bone into account. Basically, fractures result from an imbalance between internal stresses caused by loading forces and the local capacity to withstand these. A number of recent studies have suggested that combined assessment of the macroscopic geometry of the proximal femur and BMD may improve the prediction of fracture risk (21;44-48). In theory, body weight, fall distance (*e.g.* subcutaneous fat mass, length of the leg, etc), femoral neck axis length (FNAL), neck-shaft angle (NSA), neck width (NW), and radius of the femoral head (HR) could all affect the force of impact or the absorption of the energy from the fall and consequently affect the risk of hip fractures (47;49-51). A number of studies have suggested that a longer FNAL (45;51-55), larger NSA (21), and a greater NW (21;52;56) all increase the risk of HF. It is found that each centimeter increase in FNAL increases the risk of hip fracture by 50% to 80% in elderly white women (21;56). Similarly, case-control studies have demonstrated that the relative risk for HF increases by a factor of 1.3 (1.2 to 1.59) for each SD increase in FNAL (54). This thesis explores the possibility to use measurement of hip geometry to predict hip fractures.

3 Osteoporosis

3.1 Definition and diagnosis

OP is defined as *"a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk"* (57;58). In 1994, the task force appointed by the World Health Organisation suggested to define osteoporosis as a BMD more than 2.5 SD below the mean value of healthy persons of the same sex at the age of 30 years (peak bone mass) (59). Similarly, it was suggested to use term "severe osteoporosis" when the patient in addition to low BMD had one or more low energy fractures (60;61). The DXA technique has been available since 1987. In Denmark, people from approximately 50 years of age can be evaluated for their risk of osteoporosis if they fulfill one or more specific criteria (62). Sustaining a fracture of the hip, wrist, humerus, columna, or ankle by low energy trauma are among these criteria (63).

3.2 Epidemiology

Approximately 300,000 women and 75,000 men in Denmark are diagnosed with OP (64). In 1999, there were approximately 11,000 HF in Denmark (1). Two thirds of HF occurs among women. The median age in patients suffering the first HF is around 80 years (4). It is estimated that 80-90% of patients with HF older than 50 years of age suffer from OP (1). Preliminary data (29) suggest that 62% of patients low energy HF have at least one vertebral fracture and thus OP.

3.3 Prevention and treatment

The choice of treatment depends on severity of the condition, age, sex and co-morbidity as well as the etiology and national guidelines about fall prevention, healthy and “bone-friendly” lifestyle have been issued (63). The purpose of the treatment of OP is to reduce the risk of fracture – especially HF.

Non-pharmacological prevention of OP and thereby HF includes use of hip protectors (65;66), decreased alcohol and tobacco consumption (57;67-69), sufficient intake of calcium and vitamin-D through the diet or by supplementation (57;70;71), increased physical activity, and prevention of falls (13;22;57;72;73).

Pharmacological prevention and treatment options comprise drugs with antiresorptive (inhibiting osteoclast activity), anabolic (stimulating osteoblast activity) or both effects (dual action) (68;74;75). Thus, an array of drugs has been demonstrated to decrease the incidence of fractures in randomized, placebo-controlled studies. Calcium and vitamin-D alone decrease the risk of fracture (71;76) but is also used as a basis in conjunction with the specific anti-osteoporotic drugs. Bisphosphonates are antiresorptive agents that inhibit osteoclast function by inhibiting maturation of osteoclasts and increasing osteoclast apoptosis (77-80). Selective estrogen receptor modulators (SERM) are also antiresorptive, reduce bone turnover and thus the number of resorption-sites (81-83). Parathyroid hormone (PTH) increases the number of osteoblasts and thereby raises the speed of bone formation (84-86). Strontium-ranelate seems to have both anabolic and anitresorptive effects that may be mediated by the calcium-sensing receptor (87-89).

A detailed discussion on treatment of osteoporosis is beyond the scope of this thesis.

3.4 Etiology

During childhood and adolescence the bone mass increases as the skeleton grows. The maximal bone mass (peak bone mass) is achieved late in the second decade of age or early in the third decade of age, around 18 years for girls (90;91) and around 22 years for boys (92), and it remains stable until the age of about 45 years in both men and women. At this point, BMD begins to decline slowly (0.5-1%/year) (93). This *age-related bone loss* continues throughout life and seems to be related to decreasing osteoblast function as well as decreased intake and absorption of calcium in elderly men and women (94-96). During the menopausal transition women have an accelerated bone loss for a few years. This *menopausal bone loss* is related to the decreased levels of estrogen and may amount up to 5%/year (97-99). Thus, most cases of primary osteoporosis (OP) (*i.e.* post-menopausal and age-related OP) are caused by a combination of low peak bone mass, post-menopausal and age-related bone loss. Finally, secondary OP is caused by diseases or treatments (*e.g.* glucocorticoids) and may occur in both genders at all ages (95;100;101).

3.5 Genetic determinants of fracture risk

Rare cases of osteoporosis are inherited as a Mendelian disorder. Thus, the *osteoporosis pseudoglioma syndrome* caused by mutations in the gene coding for low density lipoprotein receptor-related protein 5 (LRP5) (102), *homo-cystinuria* caused by mutation in the gene coding for cystathionine beta-synthase (103), and some forms of *Ehlers-Danlos syndrome* caused by mutations in the cobber-transporting ATPase, alpha polypeptide (104) are examples of inherited osteoporosis. Similarly, several forms of osteopetrosis and osteosclerosis (*i.e.* conditions with high bone mass) are caused by mutations in the genes coding for *e.g.* LRP5 (105), chloride channel 7 (106), and cathepsin-K (107).

Family and twin studies, however, have also revealed a significant genetic influence on peak bone mass, the rate of bone loss, and the risk of developing osteoporosis in the general population (37;108-110). Indeed, 60-80% of the variance in BMD at any age is thought to be due genetics (39;110-114). The heritability of fractures *per se* seems lower and in the range of 25-35% (115-117). Nevertheless, a parental history of hip fracture results in a 2-fold increased risk of hip fracture independent of BMD (118) and the impact of genetics on BMD may explain 10-20% of the increased risk of hip fracture (108). Moreover, an array of studies has established association between a number of specific genetic polymorphisms and BMD (119-123), bone turnover (124) or fracture rates (112;124) (Table 2).

Table 2. Examples of genetic polymorphisms associated with decreased BMD, increased rate of bone loss or increased risk of fracture grouped according to biological function of the genes. Genetic polymorphisms in ***bold italics*** were studied in this thesis.

Receptors	Growth factors and cytokines	Matrix proteins	Enzymes	Miscellaneous
Vitamin-D	TGF-beta	Collagen-type-1 alpha-1	***MTHFR***	TCIRG1
Estrogen	Sclerostin	Osteocalcin	CYP19	Runx2
LRP5	OPG		Arachidonate 15-lipoxygenase gene (ALOX)	Integrin beta3
LRP6	Interleukin-6		KIT	
Calcitonin receptor	IGF1		Catechol-O-methyltransferase	
Leptin	RANKL		Farnesyl diphosphate synthase	
$P2X_7$	BMP2			
	RANK			

Only two studies have investigated hip geometry in Mendelian disorders. Patients with Marfan syndrome have increased FNAL (125). Similarly, we have reported that hip geometry is disproportionate in patients with Turner syndrome but is unlikely to account for the increased risk of fracture in these patients (126). Twin studies, however, have demonstrated that 62-79% of the variation in the FNAL may be attributable to genetic factors (37;108). Also, a recent association study in 241 families (127) demonstrated a heritability estimate for geometry of the proximal hip ranging from 30-66%. Furthermore, the same study included a genome-wide search and reported linkage with LOD-scores > 3 to regions on chromosome 15 and 22 associated to *femoral shaft section modulus*. Only few association studies regarding hip geometry have been published (Table 3) and so far, no associations have been demonstrated between the VDR polymorphisms (128) or the COLIA1 Sp1 polymorphism (124) and FNAL while the NSA was increased by about 2 degrees depending on the COLIA1 Sp1 genotypes (124).

Table 3. Genetic polymorphisms studied regarding potential associated with hip geometry. (+=significant correlation; NS= No significant correlation; ND=Not done)

Author (year)	**Genes**	**FNAL**	**NW**	**HD**	**NSA**	**Other parameters****
Cho *et al.* 2007 (129)	Nitric oxide	NS	ND	ND	ND	NS
Rivadeniera *et al.* 2006 (130)	IGF-1	ND	+	ND	ND	+
Xiong *et al.* 2005 (131)	Estrogene	ND	ND	ND	ND	+
Qureshi *et al.* 2001 (124)	COLIA1 Sp1	NS	NS	ND	+	ND
Arden *et al.* 1996 (128)	VDR	NS	ND	ND	ND	ND

** Other parameters = cross-sectional area, cortical thickness, endocortical diameter, subperiosteal width, sectional modulus, and buckling ratio.

In the present thesis, we investigated four candidate genes associated with bone mass. The gene encoding methylenetetrahydrofolate reductase (MTHFR) has been shown to affect homocysteine levels. Severe defects in – or deficiency in – or absence of the MTHFR enzyme lead to homo-cystinuria, while less pronounced enzyme defects are associated with mild to moderate hyper-homo-cysteinaemia (132). Some studies (119;133;134) have shown that patients with polymorphisms in the MTHFR gene have mild to moderate raised homocysteine levels and mildly reduced BMD while other studies have been unable to confirm this (112;135;136). Similarly, some studies (136;137) have demonstrated that the MTHFR polymorphisms are associated with increased risk of fracture, while other studies have been unable to confirm this association (112). This discrepancy may be explained by differences in folate intake (119).

Another candidate gene is that coding for the purinergic $P2X_7$ receptor which is a ligand-gated cation channel. The physiological role of the $P2X_7$ receptor in osteoclasts is only vaguely elucidated, but it seems to be involved in the signalling from osteoblasts to osteoclasts (138), and it might play important roles in regulation of osteoclast generation (139), osteoclast survival (140;141), and production of interleukin (IL)-1. (142). Two polymporphisms in this gene have been associated with ten-year fracture risk in post-menopausal women (143).

The third candidate gene is that coding for the low-density lipoprotein-receptor-related protein 5 (LRP5). It is a key regulator of bone metabolism through the Wnt signaling pathway. LRP5 is expressed by osteoblasts and regulates osteoblastic proliferation, survival and activity (144;145). Loss-of-function mutations cause the *osteoporosis-pseudo-glioma syndrome* (102;146), whereas activating mutations in this gene result in and the *high-bone-mass phenotype* (105;147), respectively. Polymorphisms in this gene

(110;144;145;148;149) have been associated with low BMD and increased risk of fracture (146;150).

4 Biomechanics (mechanical behaviour of bone)

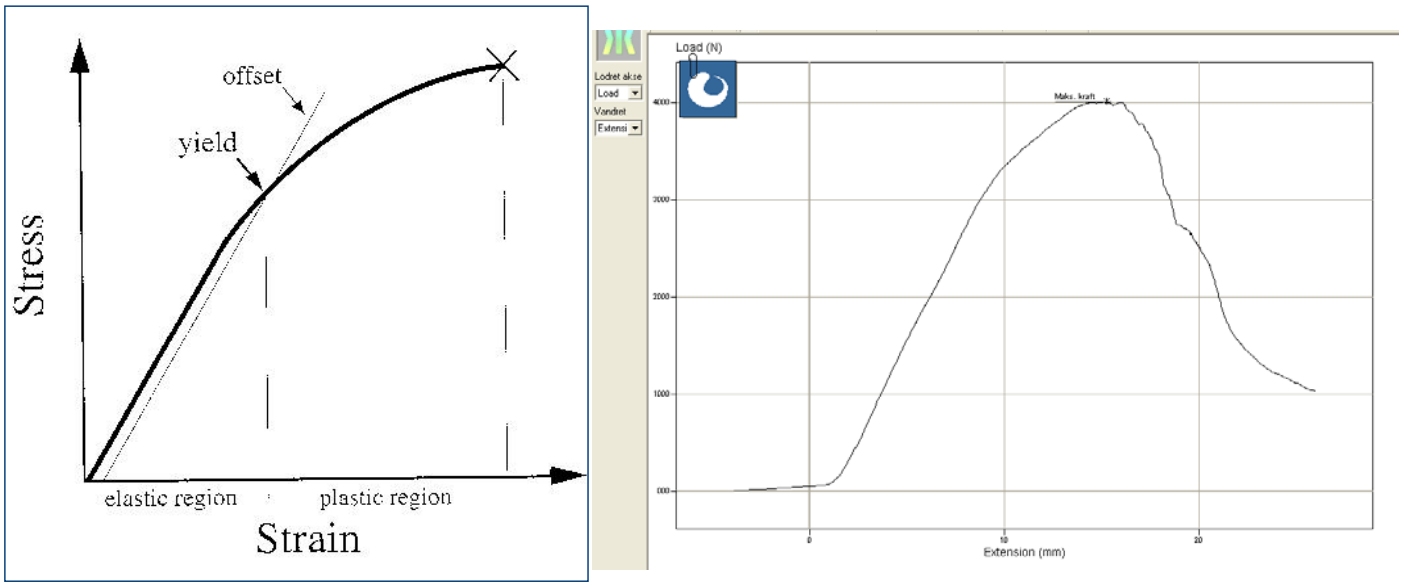
Bone has unique structural and mechanical properties that allow it to carry out functions such as stabilizing the body and adapting the physical actions acting on the human skeleton during daily activity. Bone is on of the most dynamic and metabolically active tissues in the body and remains active throughout life. For example, changes in BMD are commonly observed after periods of disuse and of greatly increased use, changes in bone shape are noted during fracture healing and after certain operations. Bone adapts to the mechanical demands by the process of *modelling* involving local bone formation and/or resorption depending upon whether the stresses are higher or lower than the “set-point”.

The human proximal femur consists of cortical bone and trabecular bone. The cortical bone constitutes about 80% of the total skeletal mass (151). It is the compact bone and the outer shell of the bone. It has two surfaces; the endosteum, which faces the bone marrow, and the periosteum, which is outside of the bone. The trabecular bone is the rest of the skeletal mass (20%) (151). The trabecular bone is the inner core of bone with the characteristic three-dimensional spongy structure. The architecture is dependent on the skeletal site and mechanical load. It can be divided into isotropic and anisotropic trabecular bone. Isotropic means that the network is equally distributed regardless of the angle from which it is observed in the three dimensional space. Anisotrophy means that the network has an orientation in the three dimensional space as in the proximal femur (151).

In biomechanics, distinction is usually made between the mechanical behaviour of a biological tissue as a *material* and the mechanical behaviour of a whole specimen as a

structure. The material behaviour of a specimen is not influenced by its geometry, and reflects the intrinsic properties of the material itself (*i.e.* intrinsic properties of trabecular and cortical bone). In contrast, the *structural* behaviour of a specimen reflects both the geometry (size and shape) as well as the intrinsic material properties of the specimen (152).

Traditionally the *material* behaviour of a specimen is determined by conducting mechanical tests on standardized specimens under controlled conditions. The material properties do not take into account the shape and geometry of the material. The density of the material is one way to describe the material properties. Also the material properties are interesting to examine if you want to learn about the stress inside the material. Stress is the internal force per unit area produced in the material in response to external loading and is measured in pascal ($Pa=N/m^2$). The stress can be applied as normal stress (perpendicular) and shear stress (angular). Strain is relative change in length of the material *i.e.* the size of deformation of the material compared to the original length of the material as a result of the applied stress The strain can be negative in compression testing and positive in tensile testing. Strain has no units of measurement and is given as a fraction. During mechanical testing, a stress-strain curve may be obtained (figure 1 A). The internal strain is divided in an elastic region and plastic region before ultimate failure.



A **B**

Figure 1: A: Stress-Strain curve from strength testing of bone-specimens. Stress is the internal force per area resulting from an external loading (Pa). Strain is the size of deformation compared to the original length of the material (152). **B:** An example of a load-deformation curve obtained during mechanical testing of cadaver bones in study-III. The applied load is on the abscissa and the deformation of the bone on the ordinate. Maximal strength before failure of the bone is indicated. Bone strength is the maximal load that can be applied before a fracture occurs.

The structural behaviour of biological tissue can be determined by conducting mechanical tests on specimens subjected to physiologic or traumatic loading conditions. It is determined from a load versus deformation curve (figure 1 B). Generally, load and deformation is linearly related until the yield region is reached, at which time the slope of the curve is reduced. Before the yield region, the structure is considered to be in the elastic region, and if unloaded, would return to its original shape. Beyond the yield region,

however, the structure undergoes permanent deformation and is said to be in the plastic region. If the load continues to increase the ultimate failure load (maximal strength) is reached, after which the structure fails (figure 2). The maximal strength is the energy stored inside the material before failure. The unit for maximal strength is Newton (1N = 1 $kg*m/s^2$). The law of elasticity of solid materials stating that here is a linear relation between the force and deformation of a solid object, however, described by Robert Hooke in 1678 (153) also applies to bone and fracture can occur any time in an individual's lifetime if the skeleton is subjected to forces that are greater than the skeleton's elastic biomechanical properties. Non-destructive assessment of bone strength, however, is complex because the biomechanical competence it is influenced by a number of different determinants such as mass, geometry, architecture, and bone tissue quality.

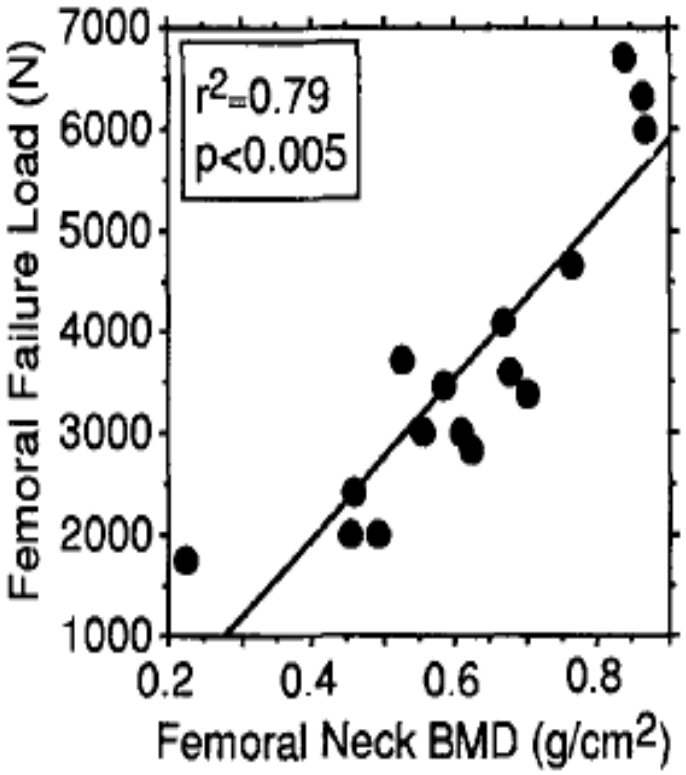


Figure 2: Femoral failure load versus femoral neck BMD. Cadaver femoral bones strength tested until fracture in sideways fall. Adapted from: Bouxsein *et al*. (38).

Moreover, a lot of assumptions must be made because the bone is anisotropic; thus the mechanical properties depend on the direction of the load applied.

As mentioned above, the dimensions of the bones are important for bone strength. Thus, the outer diameter of the long bones predicts up to 55% of the variance of the bone strength (154;155). As the long bones (*i.e.* the femur) increase in length and diameter, the cross-sectional area also increases (156). The increase in cortical thickness are largely proportional to the increase in bone diameter, thus the volumetric bone density of long bones changes little throughout childhood and adolescence (156). From the adolescence, the BMD declines with 0.5 to 1% every year (93). In women, age related bone loss accelerates around the time of the menopause for between five and ten years. This period

of accelerated bone turnover results in a decreased thickness of the longitudinal trabeculae and complete loss of some of the transverse trabeculae. The three-dimensional network of the trabeculae therefore deteriorates. The result is marked reduction in the amount and structural integrity of trabecular bone as well as thinning of cortical bone. Moreover, older bone develops an ever-increasing number of microcracks, which do not seem to heal. Bone is more prone to develop microcracks when loaded into the post-yield region. In that way, the mechanical strength of the bone declines with age. Thus, the average strength of human distal femur (157) and human vertebral bodies (158) is reduced with 47% and 74%, respectively, from the age of 20 to 80 years. The loss of strength is linear and of a magnitude of 6.7 and 10.6% per decade for the femur and vertebra, respectively (157).

The biomechanics of the hip is complex. The femoral neck has two angular relationships with the femoral shaft that are important to hip joint function. Both the NSA and the angle of ante-version secure optimal motion in the joint. NSA is in most adults about 125 degrees, but it can vary from 90 to 135 degrees (159). In cadaver studies with excised bones, it is impossible to examine the angle of the original *in situ* ante-version unless X-rays of the cadaver bones have been performed before excision. The neck shaft angle; however, can be obtained *ex vivo*.

The interior of the femoral neck is composed of trabecular bone with trabeculae organized into medial and lateral trabecular systems (152). The force applied on the femoral head under stance situations are transferred parallel to the medial system of the femur. The thin shell of cortical bone around the superior femoral neck progressively thickens in the inferior region. With ageing the femoral neck gradually undergoes degenerative changes. The cortical bone is thinned and the trabeculae are gradually resorbed (151).

5 Geometry of the hip

5.1 Measurements of the geometry

Since architecture is known to play a role in bone strength, several techniques to quantify bone architecture have been proposed. The earliest technique was the *Singh index* (SI), giving an estimate of the trabeculation in the proximal femur from CR (160). The Singh index is an inexpensive and simple technique to predict the strength of the bone (161). SI predicts the strength of the bone with significant correlation ($r=0.7$, $p<0.01$) (161-163), however, the inter-observer variation is high (161;162). Some studies (163;164) have evaluated SI in combination with DXA-scans and geometrical parameters with relatively high predictive values for predicting osteoporosis and thereby HF. Karlsson *et al.* (163) investigated this relation in a case-control study with 125 cases (92 women and 33 men) and 163 controls (93 women and 70 men). In women, the SI correlated significantly ($p<0.01$) with the BMD as measured by DXA while no correlation was found in men.

Soontrapa *et al.* (165) studied 129 HF patients but found a poor diagnostic value for osteoporosis with SI compared to DXA. The sensitivity and specificity of the SI for diagnosing osteoporosis was found to be 58% and 55%, respectively (165). Since Faulkner *et al.* (54) proposed the use of hip geometry to predict fracture risk, a large number of parameters have been reported for this use (table 4 and figure 3).

Table 4: Measures of the geometry of the proximal hip used in the literature. In this thesis, HAL in study-I corresponds to FNAL.

Parameter	Definition
HAL	Hip axis length. Length along the femoral neck axis from below the lateral aspect of the greater trochanter through the femoral neck to the inner pelvic rim
FNAL	Femoral neck axis length. Hip axis length minus the pelvic portion
NL	Neck Length. The distance between perpendicular lines which transected the hip axis length at the level of the lesser trochanter and the flare of the head
NSA	Neck shaft angle. Angle formed between the femoral neck and the shaft of the femur
NW	Neck width. Shortest distance within the femoral neck region of interest
HR	Head radius. Radius of the femoral head (study I)
Femoral head width	Diameter of the femoral head (= **HD** in study II and III)
CSA	Cross-sectional area. Total surface area of bone in the section of minimum CSMI (cross-section) within the femoral neck after excluding soft tissue spaces
CSMI	Cross-section moment of inertia. Reflects the strength and rigidity of the femoral neck when exposed to bending moments, ie a measure of one's resistance to bending
Cortical thickness	The width of cortex (measured different sites on the proximal femur)
Buckling ratio	The ratio of the outer radius of the bone to the cortical thickness
Section modulus	The CSMI divided by the distance from the neutral axis of the point of the bone to the subperiosteal surface

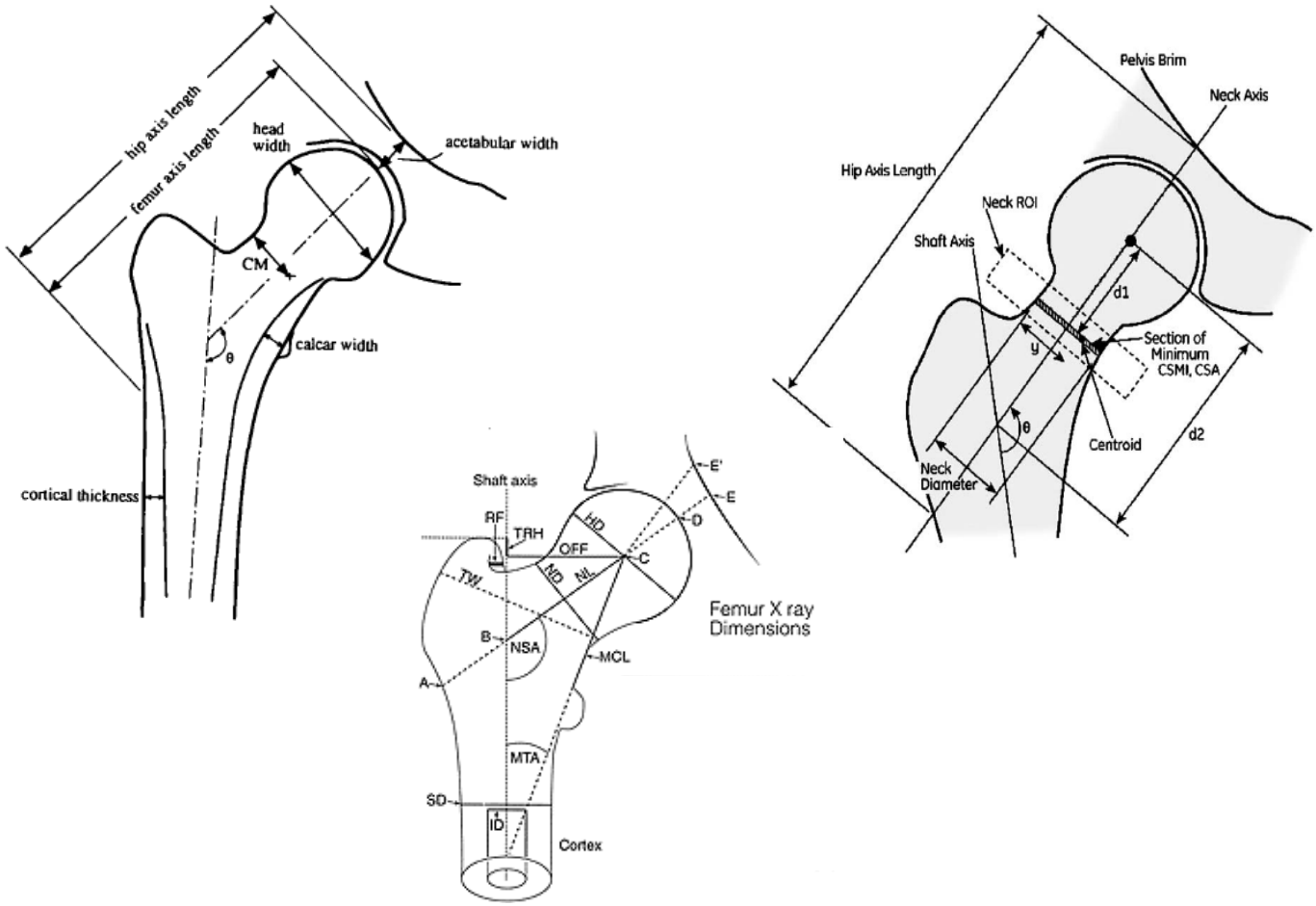


Figure 3: Outline of geometrical parameters of the hip. Adapted from Faulkner *et al.*, Michelotti *et al*., and Peacock *et al*. (54;164;166). ROI=region of interest; CSA=cross-sectional area of the femoral neck; CSMI=cross-sectional moment of inertia.

Moreover, a combination of geometrical as well as BMD measurements and derived parameters such as cross-sectional moment of inertia, cortical thickness, buckling ratio, and section modulus have been proposed. Beck *et al.* (49) developed an interactive computer program to derive femoral neck geometry from DXA-scan images for an estimate of hip strength using single plane engineering stress analysis, called “hip strength analysis” (HSA). The model depends on the edge detection provided by DXA. The software automatically measured BMD, HAL, FNAL, NSA, cross-sectional moment of inertia, cross-

sectional areas, cortical thickness, buckling ratio, and section modulus. HSA derived by DXA predicted the strength of cadaver femurs better than BMD_{nedk} (r=0.89 vs. 0.79) (49). Unfortunately, this HSA software has been unavailable for other groups until recently and the approach, therefore, has not yet been validated by independent groups. Indeed, most studies have concentrated on simple geometrical parameters such as FNAL, NW, and NSA (52;166-168). *In vivo* measurement of hip geometry can be performed in different ways. On CR the parameters of geometry can be obtained using digitizers (166) and this technique is also used on printed images from DXA-scans (21;52). Also, some groups (54;169), including our own, have developed in-house software to measure hip geometry on the screen images from DXA-scans. Engineering assumptions on DXA- and CT-scans gives the possibility to detect the boundaries between cortical and trabecular bone and between cortical bone and soft-tissue and perform the different geometrical measurements from DXA or CT images (49;54). There is no agreed consensus of definition of a number of the different parameters. For instance, some authors measure HAL as the length from trochanter to the medial aspect of the femoral head (52;166-168) while others use the term FNAL for this and measure HAL from the trochanter to the inner pelvic rim (126;166;168) (table 4).

Another way to estimate the strength of the proximal femur is *finite element analysis* (FE). This approach is based on mathematical assumptions and measurements by 3D CT or 2D DXA (170;171). The 3D or 2D reconstruction is transformed into an equally shaped finite element model by simply converting all bone voxels or pixels to equally sized brick elements (34;172). Assuming the material strength of each brick the theoretical strength estimation of the whole bone can be derived (171;172). The maximal strength of the proximal femur was found to correlate more closely with FE (r^2=0.84) than DXA (r^2=0.57) in

a study by Cody *et al.* (34). Similar correlation between FE and maximal strength (r^2=0.93) was reported by Keyak *et al.* (173). Schileo *et al.* (174) compared three different FE-models, and found r^2 values from 0.55 to 0.91. Thus, FE is still not standardized, it is time consuming and the method needs to be more extensively evaluated before implemented in clinical use.

5.2 Association between hip geometry and maximal strength

Table 5 outlines previous studies investigating the association between hip geometry and maximal strength of the hip in mechanical testing. The majority of the studies used freshly harvested cadaveric human proximal femora. Specimens were tested fresh or defrosted while securing the humidity of the preparation. Eckstein (175;176), Bauer (177), Pulkkinen (178), and Lochmüller (179), working in the same group, all used formalin fixated cadaver bones. Also, most studies imitated a sideways fall. Only few of the studies tested the maximal strength in the stance situation. All studies used a set-up simulating 15^o anteversion in the hip. Furthermore, the load was applied either on the femoral head or on the throchanter major. The background for choosing these test conditions is not discussed in all the studies. A common limitation of the studies, moreover, is the limited access to cadaveric material. This decreases power and limits the possibilities of experimentation with the set-up. The studies used a wide range of loading rates no matter if the set up was testing fall or stance-situation. The study by Bousson *et al.* (180) tested the stance situation with 762 mm/s (12.7 mm/min) while Bouxsein *et al.* (181) tested the specimens with 100 mm/s. These values should be compared with the calculated speed at impact during a fall on the greater trochanter of 330 mm/s calculated by Askegaard *et al*. (182).

Table 5: *In vitro* studies on hip geometry. Relevant studies from the following search-terms in PubMed were used: human, proximal hip, geometry, prediction, fracture, risk, cadaver, in vitro. Significant correlation are shown as r^2 values; NS= No significant correlation; ND=Not done; St=Stance; Sf= Sideways fall). *No R^2-values stated in the paper.

	Patients			**Specimens and testing**			**Correlation with maximal strength**				
Author, year	**N**	**Sex**	**Mean age or range (Years)**	**Storage and fixation**	**Loading rate**	**Loading pattern**	**FNAL**	**NW**	**HD**	**NSA**	**BMD**
Bouxsein *et al.* 2007 (181)	21 42	♀ cases ♀ controls	74 74	Fresh and frozen	100 mm/s	Sideways fall	ND	ND	ND	ND	0.82
Bauer *et al.* 2006 (177)	62 57	♀ ♂	80 80	Formalin	6.6 mm/s	Sideways fall	0.36	ND	ND	ND	0.68
Pulkkinen *et al.* 2006 (178)	77 63	♀ ♂	82 79	Formalin	6.6 mm/s	Sideways fall	ND	ND	ND	0.15	+ *
Bousson *et al.* 2006 (180)	23 5	♀ ♂	84 84	Fresh and frozen	0.2 mm/s	Stance	NS	ND	ND	ND	0.67
Ecksteinn *et al.* 2004 (176)	30 24	♀ ♂	79 79	Formalin	6.6 mm/s	Sideways fall	ND	ND	ND	ND	0.79
Ecksteinn *et al.* 2002 (175)	72 38	♀ ♂	81 81	Formalin	6.5 mm/s	Stance and sideways fall	ND	ND	ND	ND	St 0.69 Sf 0.77
Lochmüller *et al.* 2002 (179)	63 42	♀ ♂	82 76	Formalin	6.5 mm/s	Stance and sideways fall	St 0.27 Sf 0.17	ND	ND	ND	+*
Cody *et al.* 1999 (34)	23 28	♀ ♂	42-93	Fresh, frozen	0.21 mm/s	Stance	NS	NS	+*	ND	0.56
Cheng *et al.* 1997 (183)	28 36	♀ ♂	71 67	Fresh, frozen	14 mm/s	Sideways fall	0.24	0.22	ND	NS	0.88
Lang *et al.* 1997 (184)	8 5	♀ ♂	73 73	Fresh	0.5 mm/s	Stance and sideways fall	+*	ND	ND	ND	St 0.93 Sf 0.87
Bouxsein *et al.* 1995 (38)	6 10	♀ ♂	76 76	Fresh, frozen	2 mm/s	Sideways fall	0.27	ND	ND	ND	0.79

All *in vitro* studies found significant correlation between the maximal strength and BMD with r^2 in the range from 0.56 to 0.93. Both in stance and sideways fall loading conditions correlations were significant. Significant correlations were in some studies (175;177;180;181) found between maximal strength and BMD both in the total, the trochanter, and the neck regions ($p<0.05$). Some studies (176;178), however, only measured BMD_{tot}. Other studies measuring all BMD-values found the closest correlation with BMD_{neck} (34;184) and BMD_{troch} (183;184). In the published studies, FNAL was measured in different ways while the other geometrical parameters were measured in only few studies (34;178;183). All studies but two (34;180) found positive correlation between maximal strength and FNAL with r^2-values ranging from 0.17 to 0.36. Combining BMD and FNAL was found to be highly predictive of bone strength (175;184). Thus, Lang *et al.* (184) found that the combination of BMD_{troch} and FNAL explained approximately 90% of the variance in maximal strength, while others found models explaining from 52% (combination of BMD_{neck}, HAL, cortical moment of inertia, and trabecular density) to 57% (only BMD_{neck}) (34;179). Karlsson *et al*. (163) measured FNAL, NW, and NSA on DXA and on CR and found significant correlations in predicting HF for both DXA and CR respectively, however not in NSA. There was significant correlation for measuring FNAL by DXA and by SI ($r=0.37$, $p<0.001$). Generally, the *in vitro* studies were carried out in elderly patients aged 71 to 84 years at death. The studies varied in size from 13 to 140 patients.

5.3 Clinical studies

Sustaining HF is a result of a cascade of events after a fall (figure 4).

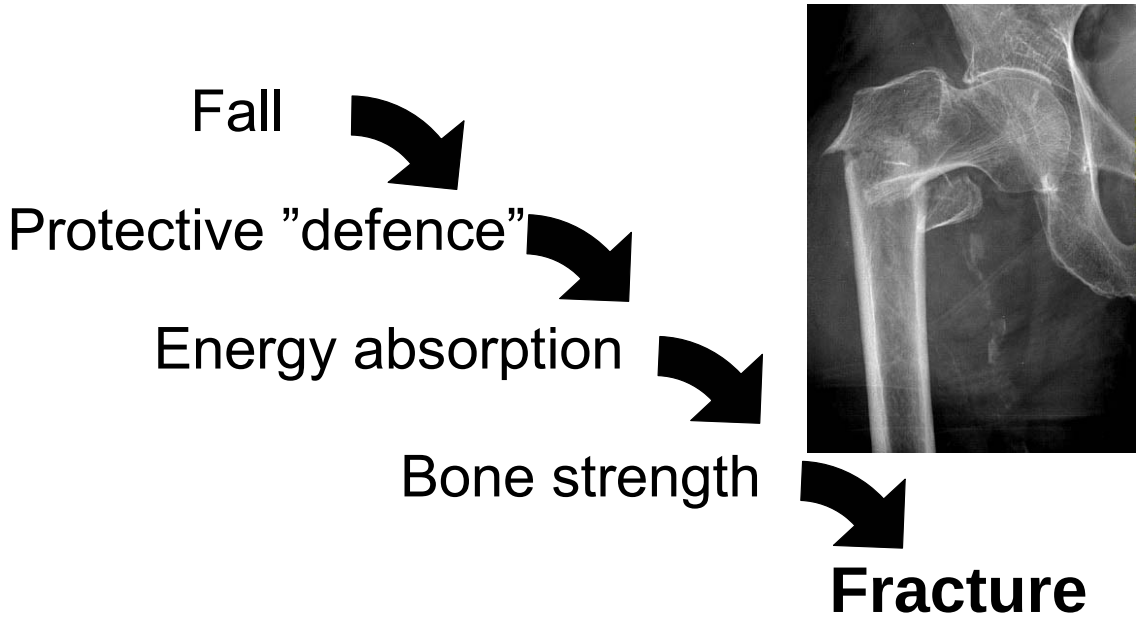


Figure 4: The fall-cascade. Before fracture occurs, several protective mechanisms have to fail.

Table 6 lists the clinical studies reporting on the association of hip geometry with fracture risk. Most of these have been case-control studies, while a few were designed as nested case-control studies (45;53;185;186). The majority of the studies included relatively few patients (less than 100) and even fewer (around 50) age-matched controls. Only a few studies included more than 150 participants in the control group (21;45;53;54;56;185;187;188). The majority of the patients were women. The age of the patients was around 80 years while the controls tended to be younger in many studies (21;45;54;56;187-189). Only few studies (33;53;55;168;169;185;189;190) differentiated between the types of HF but if so, the most frequent fracture type was neck HF. The

geometrical measurements was acquired using digitizers on X-rays, digitizers on images from DXA-scans, special software on the screen images of DXA-scans, or measurements calculated from software on reconstructed CT images. All case-control studies found that the odds-ratio for fracture correlated significantly with BMD. Most studies measured FNAL, while only few studies (21;52;53;56;166;168;185;188;190;191) included other geometrical parameters (*e.g.* NW, HD, and NSA). FNAL was not significantly correlated with the risk of fracture in all the studies (21;33;166;169;186). A number studies have suggested that a longer FNAL (45;51-55), larger NSA (21), and a greater NW (21;52;56) all increase the risk of hip fracture. Thus, Crabtree *et al.* (45) found that FNAL was increased in 68 patients with previous HF compared with 800 controls. In contrast, Duboeuf *et al*. (53) demonstrated an increased FNAL in 42 women with cervical but not in 24 women trochanteric fractures compared with 167 controls. Furthermore, a number of studies (21;166;169;186) found no difference between the groups regarding FNAL, and a single study (189) even found a shorter FNAL in patients with HF.

Table 6: Case-control studies on hip geometry. The following search-terms were used: human, proximal hip, geometry, prediction, fracture, risk, prediction, in vivo. +=significant correlation (OR=Odds-ratio); NS= No significant correlation; ND=Not done; NHF=Neck HF; THF=Trochanter HF

Author Publication year	Type of study	Cases (n) Mean age	Controls (n) Mean age	Fracture type	Methods	HAL	NW	HD	NSA	BMD	Out-come measures
Cheng *et al.* 2007 (33)	Case-control	45 ♀ 75 years	66 ♀ 71 years	34 NHF 11 THF	QCT	NS	ND	ND	ND	+ OR=6.8	BMD_{vol} compared to BMD_{area}
Riancho *et al.* 2007 (191)	Case-control Cross-sect	871 ♀+♂ 51 years	19 ♀ 69 years	ND	DXA HSA-software	ND	NS	ND	ND	+ *	Volumetric BMD
Faulkner *et al.* 2006 (54)	Case-control	365♀ 71 years	2141♀ 66 years	ND	DXA HSA-software	+ OR=1.3	ND	ND	ND	+ OR=2.0	Geometry, CSMI, Femoral strength index
Szulc *et al.* 2006 (185)	Case-control	65 ♀ 82 years	167 ♀ 80 years	42 NHF 23 THF	DXA	+ OR=1.6	NS	ND	ND	+ OR=2.5	Geometry and BMD in NHF and THF
Patton *et al.* 2006 (168)	Case-specific	50 neck HF 50 trochan.HF (4♀/1♂ 82 years /75 years)	Comparison between neck HF and trochan HF	50 NHF 50 THF	X-ray	+*	NS	NS	ND	ND	Diff in geometry in relation to HF-type

Author Publication year	Type of study	Cases Age (mean)	Controls Age (mean)	Fracture type	Methods	HAL	NW	HD	NSA	BMD	Out-come measures
El-Kaissi *et al.* 2005 (56)	Case-control	62♀ 78 years	608♀ 74 years	ND	DXA HSA-software	+ OR=1.7	+ OR=2.4	ND	ND	+*	Geometry and DXA Cortical thickness
Frisoli *et al.* 2005 (55)	Case-control	46♀ 76 years	66♀ 77 years	31 NHF 15 THF	DXA HSA-software	+ OR=2.2	ND	ND	ND	+ *	Anthropometric data, BMD, HAL
Gnudi *et al.* 2004 (188)	Case-control	134♀ (hip) 77 years	491♀ 74 years	134 NHF	DXA HSA-software	+ OR=1.5	ND	+ OR=1.3	+ OR=1.7	+ OR=2.3	Geometry and DXA Can geometry of HF predict spinefx,
Duan *et al.* 2003 (187)	Case-control	180♀ 75 years 127♂ 76 years	187♀ 70 years 134♂ 72 years	ND	DXA HSA-software	ND	ND	ND	ND	+*	BMD, strength, geometry CSMI, fem.neck fragility
Bergot *et al.* 2002 (52)	Case-control	49♀ 68 years	49 ♀ normal BMD 49 ♀ low BMD 68 years	49 NHF	DXA, digitizer	+*	NS	ND	NS	+*	Site of BMD and geometric parameter to predict HF
Crabtree *et al.* 2002 (45)	Case-control	68♀ 78 years	800♀ 69 years	ND	DXA HSA-software	NS	ND	ND	ND	+ 0.83 Area under ROC	BMD, strength, geometry
Partanen *et al.* 2001 (190)	Case-control	70♀ 80 years	40♀ 80 years	46 NHF 24 THF	X-ray, digitizer	ND	+*	ND	+*	ND	Diff in geometry in relation to HF-type

Author Publication year	Type of study	Cases Age (mean)	Controls Age (mean)	Fracture type	Methods	HAL	NW	HD	NSA	BMD	Out-come measures
Alonso *et al.* 2000 (21)	Case-control	295♀ 75 years 116♂ 75 years	310♀ 70 years 235♂ 70 years	Divided in intra and extra capsular (no calc. between controls and fracturetype)	DXA, digitizer	NS	+ ♀ OR=2.4 ♂ OR=2.1	ND	+ ♀ OR=3.5 ♂ OR=2.5	+ ♀ OR=4.5 ♂ OR=4.5	BMD and geometry and the role in prediction of HF
Pande *et al.* 2000 (169)	Case-control	62 ♂ 78 years	100 ♂ 75 years	31 NHF 31 THF	DXA Geometry	NS	ND	ND	ND	+ OR=4.2	HAL and BMD in men
Michelotti *et al.* 1999 (166)	Case-control	43 ♀ 73 years	119 ♀ 73 years	ND	X-ray	NS	+*	+*	ND	ND	Geometry
Parkkari 1999 (19)	Case-control	206♀ 80 years	100♀ 79 years	ND	Interview	ND	ND	ND	ND	ND	What kind of fall lead to HF
Dretakis *et al.* 1999 (189)	Case-control	78 ♀ . 76 years	117♀ (and 40 agematched) 67 years	38 NHF 40 THF	DXA Geometry	+*	ND	ND	ND	+*	Geometry, BMI and BMD
Center *et al.* 1998 (186)	Case-control	23♀ 77 years 13♂ 77 years	100♀ 76 years 114♂ 75 years	ND	DXA HSA-software	NS	ND	ND	ND	+ ♀ OR=2.5 ♂ OR=3.2	BMD, strength, geometry
Duboeuf *et al.* 1997 (53)	Case-control	42♀ NHF 80 years 24♀ THF 83 years	167 ♀ 80 years	42 NHF 24 THF	DXA Geometry	Neck: + (OR=1.6) Troch: NS	Neck: NS Troch: + (OR=1.5)	ND	ND	+ OR=2.8	Diff in geometry in NHF and THF BMD

6 Aims of the thesis

The purpose of the present thesis was to investigate the potential use of measurements of the macroscopic geometry of the human proximal femur to predict the risk of HF. Moreover, we wanted to investigate the relative power of geometric parameters and BMD in that respect. We hypothesised that:

- The geometrical parameters are independent of sex, age, body height, body weight, menarche age, and age at menopause.
- Polymorphisms in genes known to affect BMD (*i.e.* MTHFR, $P2X_7$ and LRP5) are associated with the geometry of the proximal femur.
- The maximal strength of the proximal femur as tested post-mortem is independent of BMD and the geometrical parameters.
- Geometrical parameters of the proximal hip, BMD, and the combination of these do not differ significantly between patients with hip fracture and controls.

7 Patients and methods

7.1 Patients

In the first paper, healthy men and women were included by advertisements in factories, university, police, fire brigades, and senior citizen clubs, etc. All the information concerning the participants was collected by a semi-structured interview. Eighty-five (54%) of the women were pre-menopausal and 68 (46%) were post-menopausal. Participants were eligible for inclusion, provided they were above 18 years of age. Persons were excluded in case of metabolic bone disease including non-traumatic fractures (including femoral neck fractures), abnormal renal function, current or past malignancy, newly diagnosed or uncontrolled chronic disease, alcohol or drug addiction, diabetes, hip or knee arthroplasty, prolongated immobilization, resection of the ventricle or the small bowel. Also, current or past treatment with glucocorticoids, anti-epileptics, or anti-coagulants for more than 6 months, current treatment with diuretics, currently or past use of bisphosphonate, fluoride, or calcitonin out-ruled participation. Moreover, women were excluded in case of pregnancy, current or previous estrogen use, menopause before the age of 40 years, oophorectomy, or hysterectomy. The subjects were participating in an ongoing study on different aspects of bone metabolism in healthy individuals.

In the second paper included patients participating in The Danish Osteoporosis Prevention Study (DOPS). This was a nation-wide longitudinal multi-centre study on risk factors for osteoporosis. From 1990 to 1993 a total of 2016 healthy peri-menopausal women were included in DOPS. The study was open and comprised a randomized (hormone replacement therapy (HRT) or no treatment) and a non-randomized arm (HRT or not by personal choice). Women were eligible for inclusion, provided they were 45-58 years of age and peri-menopausal. Participants were excluded if they have

experienced non-traumatic fractures, or suffered from malignancy, or uncontrolled chronic diseases. The present paper comprised baseline data on 800 women included in DOPS in Odense and Aarhus in whom DNA analysis could be performed. None of the participants received hormone therapy.

In the third paper, we included specimens from 38 recently diseased patients aged 30-68 years collected in the period from 1995 to 1996 during forensic autopsy. Proximal femur was excised during autopsy. Patients were eligible for inclusion, provided the person were above 18 years of age and had an intact hip. The exclusion criteria included non-traumatic fractures, or suffered from malignancy, or uncontrolled chronic diseases were known metabolic bone disease including non-traumatic fractures (including femoral neck fractures), abnormal renal function, current or past malignancy, newly diagnosed or uncontrolled chronic disease, alcohol or drug addiction, diabetes mellitus, prolongated immobilization, resection of the ventricle or the small bowel. Also, current or past treatment with glucocorticoids, anti-epileptics, or anti-coagulants for more than 6 months, current treatment with diuretics, currently or past use of bisphosphonate, fluoride, or calcitonin out-ruled participation. Information was based on hospital records and police reports.

Finally, in the fourth paper we included 162 consecutive elderly women recently suffering low-energy HF referred for evaluation regarding osteoporosis as part of clinical routine (*fracture discharge program*). The fractures had all been treated by osteosynthesis (screw fixation) or hemi-arthroplasty depending on the type of fracture. Dementia, severe co-morbidities, and pathological fractures out-ruled participation. Clinical information was collected from the hospital records and questionnaires. The control group consisted of 248 healthy women aged 55 to 79 years invited by letter using data from the

Danish central personal register and participating in an ongoing study on osteoporosis and ultrasound (OPUS). The invited women were not included in OPUS if they had previous bilateral fractures of calcaneus or hip prosthesis or cognitive impairment.

7.2 Methods

7.2.1 DXA-scan

In study I and II we performed dual-energy X-ray absorptiometry (DXA) of the right hip using a Hologic® 1000 osteodensitometer (Hologic® 1000, Inc., Waltham, MA) with standardized medial rotation of the femur to 15^{o}. Pencil-beam scan mode was used. To standardize and secure low repositioning variation coefficients a footplate supplied by the manufacturer was used during the scan to standardize the medial rotation of the femur.

In study III, DXA was performed using a Hologic® 2000 osteodensitometer (Hologic, Inc., Waltham, MA) with pencil-beam scan mode. During scans the specimens were still frozen, wrapped in plastic bags, and placed in a box with rice to simulate soft tissue and to standardize the medial rotation of the femur to 15^{o} in order to obtain correct anatomical position.

In study IV, DXA of the un-fractured hip in the case-group was performed using a Hologic® Discovery® osteodensitometer (Hologic, Inc., Waltham, MA) with fan-beam scan mode. The right hip was scanned in the control-group. Similar we used a footplate supplied by the manufacturer during the scan to standardize the medial rotation of the femur to 15^{o}.

The radiation dose from a DXA-scan is low, *i.e.*.0.5-5 µSv compared with absorbed dose from the natural background radiation of approximately 2 µSv/year. The volumetric BMD of the femoral neck (BMD_{vol}) (study II and III) was calculated assuming that the femoral neck region is a cylinder with a diameter using the formula: BMD_{vol} =

$BMC_{neck}/(\pi*(NW/2)^2*1\ cm)$ (191).

7.2.2 Geometry

In studies I-III, hip geometry, *i.e.* femoral neck axis length (FNAL), neck-width (NW), neck-shaft-angle (NSA), and femoral head-radius (HR) in study I, and femoral head-diameter (HD) in study II-III were measured on the screen of the DXA-scans using in-house software taking in to account the lines defined by the Hologic software. The operator placed the points and the co-ordinates were stored by the software. Distances and angles were calculated using SPSS (Statistical Package for Social Sciences). We defined FNAL as the length from the greater trochanter to the top of the femoral head through the neck-line, set by the Hologic software (in study I FNAL was called HAL). NW, NSA, and HR were also measured. See details in figure 5. Using CT-scans of cadaver-bones, we obtained the true dimensions for enlargement factor by direct measurement for comparison. The intra-observer coefficients of variation regarding measurements on the acquired images were 0.81% for FNAL, 0.53% for NSA, 1.40% for NW, and 5.16% for HR. The inter-observer coefficients of variation were 0.84% for FNAL, 0.60% for NSA, 0.80% for NW, and 7.56% for HR. Both calculated from repeated measurements on 15 subjects. Moreover, 10 patients had two DXA-scans on the same day following repositioning. The variation coefficients from these measurements were 0.66% for FNAL, 1.29% for NSA, 4.10% for NW, and 5.87% for HR. The pixel size and hence, the resolution on the screen was 22 pixels pr mm (192).

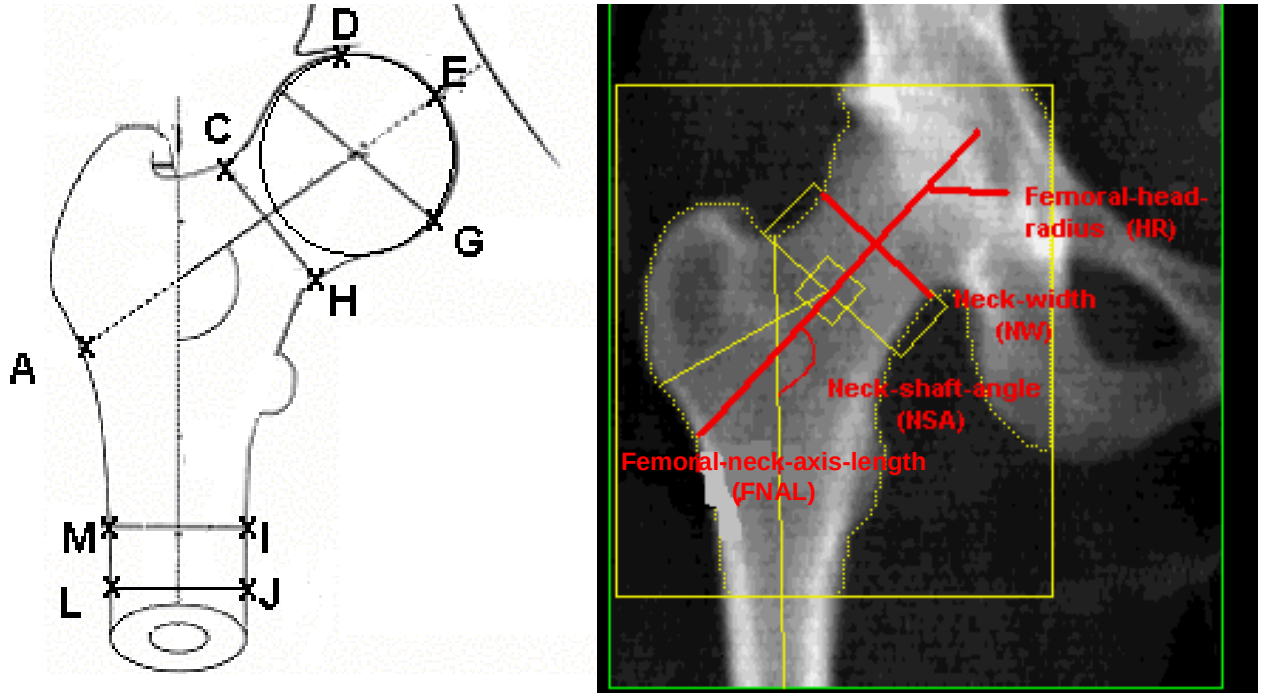


Figure 5: Outline of the geometrical measurements performed on DXA-images by help of lines set by Hologic software. **Right:** Yellow lines indicate standard regions of interest and femoral axis while red lines indicate FNAL, NW, NSA, and HR (HD=2*HR) as measured by our in-house software on the screen images. **Left:** Femoral neck axis length (FNAL) is the length from the greater trochanter to the top of the femoral head through the neck-line, set by the Hologic software, (A-E) and Neck width (NW) is the width of the femoral neck through the proximal line of the neck square, set by the Hologic software, (C-H). We calculated the Neck shaft angle (NSA) as the angle between the neckline, corresponding to A-E, and a line through the shaft of the femur calculated and adjusted by the midpoints of (I-M) and (J-L), which were all set on the outer cortex of the femoral shaft below the region of interest, set by the Hologic software. D, E, and G were all placed on the outer rim of the caput femora giving the peripheral marks of a circle and used for the calculation of head radius (HR). HD= 2X*HR.

In study IV, hip geometry, *i.e.* FNAL, NSA and NW (defined as narrow neck width), was measured using the Hologic APEX-Hip Structure Analysis-software® as illustrated in figure 6. The inner rim of the pelvic rim was secured to be inside the region of interest.

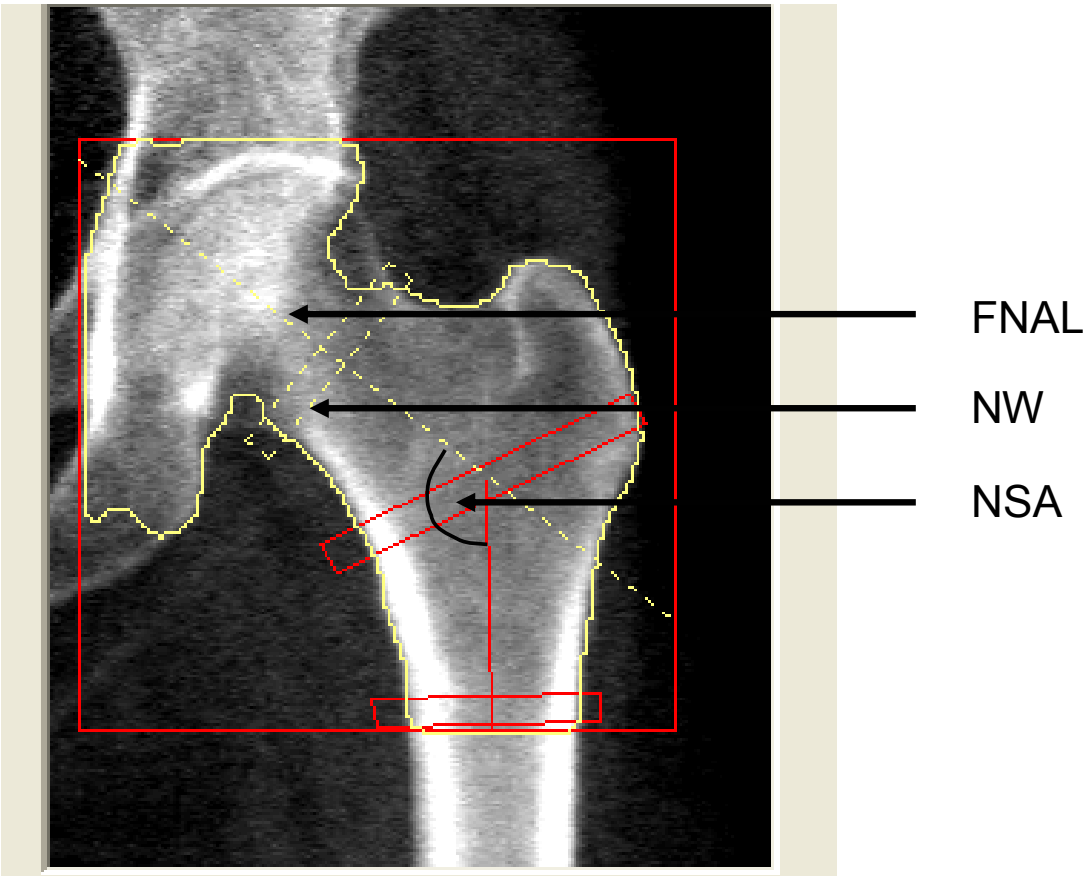


Figure 6: Region of interest used in the Hip Structure Analysis. The yellow dashed line marks the FNAL from the inner pelvic rim to the outer cortex. NSA measured by help of the red vertical line. NW measured from the dashed yellow neck-box.

7.2.3 Classification of hip fractures

The fractures discussed in study IV, were defined as fractures caused by fall from a standing height or less or due to simple actions such as bending forward. HFs were classified in to three groups – medial, pertrochanteric, and subtrochanteric according to standard criteria given by radiologists (193;193) (figure 7).

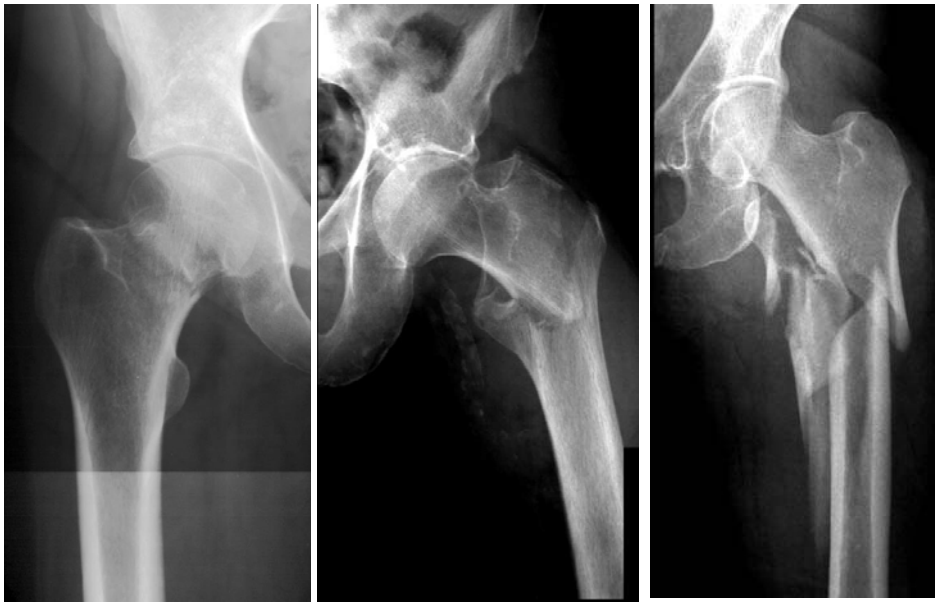


Figure 7: Showing from left to right: medial, pertrochanteric, and subtrochanteric HF.

7.2.4 Polymerase Chain reaction (PCR)

The DNA was extracted from leukocytes by ammonium acetate precipitation. The Polymerase Chain reaction (PCR) was used to selective amplification of the target DNA sequences by the use of specific oligonucleotides (primers) designed to delimit the fragment of interest. These primers were added to the denatured template DNA, and thus binding specifically to the complementary sequences at the target site.

This thesis concerned four different gene variations. The MTHFR c.677C>T polymorphism polymorphism was analyzed as described by Morita et al (194). Regarding the P2X7

(Glu496Ala) and the P2X7 (Ile568Asn) polymorphisms, a primer pair was designed to anneal at intron sequences flanking exon 13 of P2X7 in order to ensure that the whole exon would be sequenced. The polymorphisms were then analyzed by help of two restriction fragment length polymorphism assays. The LRP5 exon 9 (c.266A>G) polymorphism was genotyped using TaqMan allelic discrimination assays (143).

The genotyping was performed in laboratories in Odense, Aarhus and Hvidovre.

7.2.5 Autopsy

The specimens were cut off the proximal femur, just below the minor trochanter, surrounding soft tissue was removed, and the specimens were wrapped in 2 plastic bags to prevent dehydration, and stored at -20^0C until analysis. The time from death to forensic autopsy ranged from 1 to 3 days.

7.2.5 Mechanical testing

Mechanical testing was performed using a Lloyd LR 50K machine (Lloyd instruments, Hants, UK). Specimens were thawed in a 22°C isotonic sodium-chloride solution for twenty-four hours. During testing, the specimens were fixed with six screws in the femoral shaft to ensure 15^0 ante-version of the collum and 10^0 varus-positioning of the femoral shaft mimicking the position of the proximal hip in a fall on the greater trochanter (figure 8).

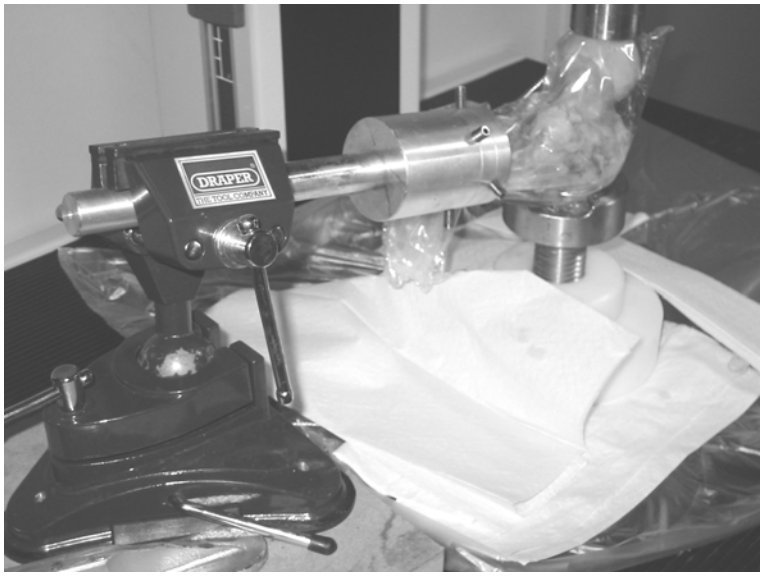


Figure 8: The test setup mimicking the position of the proximal hip in a fall on the greater trochanter.

No movement of the specimen during testing was allowed. No padding was used to simulate the soft tissue. Specimens were kept humid during testing. The specimens were tested with a constant speed of 2 mm/min and increasing load until fracture and the load at failure was noted as maximal strength. Failure was recognized as a sudden drop in sustained load, often accompanied by an audible crack. The resulting type of hip fracture (trochanter, neck or other) was determined by X-rays (figure 9).

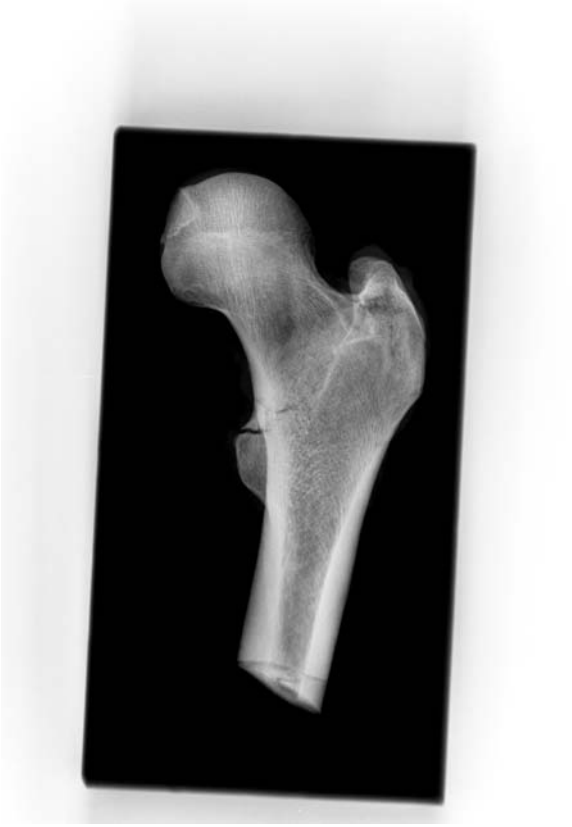


Figure 9: Example of a trochanteric fracture of the proximal femur resulting from mechanical testing (study III).

8 Ethics

All patients included in study I and II received oral and written information concerning the study before giving written informed consent. The protocols were approved by the Aarhus County Ethical Scientific Committee. The *in vitro* study (study III) was approved by the Aarhus County Ethical Scientific Committee. The fourth study included patients (cases) seen as part of clinical routine. The controls were participating in an ongoing study approved by the Ethical Committee for Vejle and Fuenen Counties. They received oral and written information concerning the study before giving written informed consent.

9 Statistical methods

All statistical calculations were performed using the SPSS for Windows version 10.0 (SPSS, Inc., Chicago, IL, USA). Normally distributed data were presented as means ± SD. Data on age were presented as median [range]. Comparisons between groups were performed using independent samples T-test. We examined the influence of the height, weight, age, and BMD-values on the geometrical parameters by Pearson correlation analysis in the healthy or genotypic normal populations. To investigate the relationships between geometrical parameters of the hip and anthropometric and other relevant data we used either Pearson correlation analysis or one-way-ANOVA. To obtain models explaining and discriminating ex strength or cases and controls we used multiple (backwards) regression analysis or multiple binary logistic regression analyses (backwards). P-values less than 0.05 were considered significant.

10 Studies in the thesis

10.1 Study I

Geometry of the Proximal Femur in Relation to Age and Sex

A Cross-Sectional Study in Healthy Adult Danes

10.2 Study II

No association between hip geometry and four common polymorphisms associated with fracture

The Danish Osteoporosis Prevention Study

10.3 Study III

Femoral neck axis length predicts bone strength in the proximal femur

A human autopsy study

10.4 Study IV

Femoral neck axis length is increased in patients with previous hip fracture

A case-control study.

11 General discussion

This thesis presents several new findings and supports previous studies regarding several issues. First, we showed the existence of significant sex-specific differences in the geometrical dimensions of the proximal femur in the Danish population. Not surprisingly, we found that hip dimensions were significantly larger in men compared with women. Furthermore, we showed in study-I that body height correlated significantly with FNAL, NW, and HD in both genders. Similar correlation between the four geometrical parameters and body height was demonstrated in study-II and in study-III regarding FNAL and HD. In study-IV, we only found significant correlation between FNAL and body height. Second, we established normal reference data regarding Caucasians of Danish decent on for future clinical use and use in clinical studies. Third, we investigated the potential association between hip geometry and four different polymorphisms known to be associated with an increased fracture incidence and/or reduced BMD in a large Danish population of healthy women. We were, however, unable to demonstrate association between hip geometry and any of the tested polymorphisms. Fourth, we showed (study-III) that FNAL independently and significantly predicted the maximal strength of the human proximal femur. FNAL alone explained 46% while models including both FNAL and BMD_{neck} explained 62% of the variation in maximal strength. In contrast, no significant correlation between NW, HD and NSA and maximal strength could be demonstrated. Finally, we demonstrated (study-IV) that FNAL and NW of the human proximal femur were significantly increased in patients with recent hip fracture.

We focused on simple geometrical parameters of the proximal femur previously suggested to be associated with fracture risk *i.e.* FNAL, NW, NSA, and HD (21;45;51-56). These parameters are easy to measure on X-rays or DXA-scans, however,

both of these techniques are 2-dimensional. The diameter of true cylinders and spheres may be assessed without bias from 2-dimensional images and it is fair to assume that the proximal femur is a cylinder and the femoral head a sphere. Measurement of the length of objects (e.g. FNAL), and angles (e.g. NSA), however, may be subject to bias depending on rotation. In these cases, only 3-D images (*e.g.* CT-scans) may provide unbiased measurements. Great care was taken, however, to ensure correct and fixed positioning of patients and specimens during DXA-scans in the studies. Indeed, the intra- and inter-observer CVs were low. In the future, 3-dimensional DXA-scans may become available and solve these problems.

In studies I-III, we used pencil-beam scanning mode which eliminates the enlargement factor inherent to fan-beam devices and to plain X-rays. In study-IV, we were forced to use fan-beam scan mode as this is the only currently available method (195;196). This may introduce an enlargement error of 7% (195;196). Although, elevation of the object of interest above the table (*e.g.* due to subcutaneous fat or muscle tissue), may affect the enlargement, this effect is small and unlikely to bias our results and conclusions.

In our studies, we relied on the edge-detection of the DXA-scanner to delineate the bone contour. The resolution on the screen was 22 pixels pr mm, however artifacts such as calcifications in arteries around the femur presented a problem in a few cases. Moreover, we developed in-house software to determine the coordinates on the screen image. Other investigators have used a digitizer (21;52) or simple rulers (166;168;178) to measure geometrical parameters. The techniques are all used in different studies (21;49;53;126;153;166-168) and there are no consensus in the methods.

Furthermore, some of the methods such as the HSA software developed by Beck *et al.* (49) have just recently become commercially available and thus remain to be validated.

In study I-IV, we measured FNAL to be 10.8 ± 0.7 to 10.9 ± 0.7 cm in men and 9.3 ± 0.6 to 10.9 ± 0.6 cm in women in correspondence with other studies (54;166;177;186). Also, the differences in between genders are supported by others (21;44;97). We found NW to be 3.8 ± 0.3 to 4.0 ± 0.3 cm in men and 3.4 ± 0.3 to 3.8 ± 0.3 cm in women which is also in agreement with other studies (21;52;183). In studies I, II, and IV, we found NSA to be 127 ± 6 to 131 ± 6 degrees in men and 127 ± 6 to 129 ± 6 degrees in women. Other studies (21;47;183;190;197) support our findings on these measurements. We, however, found a negative correlation between NSA and age in study III. In study I (192), moreover, we found significantly smaller NSA in post-menopausal compared to pre-menopausal women (128 ± 5 vs. 130 ± 4 degrees, $p<0.001$). The significant negative correlation between age and NSA found in study-III could not be demonstrated in the other studies in this thesis, however, a similar relationship has been reported in other studies (47;190). In study I-III HD was measured to be ranging from 4.8 ± 0.3 to 5.0 ± 0.3 cm in men and 3.8 ± 0.4 to 4.6 ± 0.2 cm in women. These findings also corresponds to other findings (166;168;190). Some of the differences in measurements of HD may be explained by the overlay of acetabulum on 2D-images or arthrosis of the hip joint disturbing edge detection.

We were unable to demonstrate association between hip geometry and any of the tested polymorphisms. Twin studies have demonstrated that FNAL is hereditable (37;108), although, one study (114) suggested a low heritability index. Also, genome-wide association studies (127;198) have demonstrated significant association with specific chromosomal regions and FNAL, NSA, and NW. Like our study, previous association studies have been negative (124;128;129). This underscores the main drawback of the

candidate-gene approach. The number of possible genes to test is enormous and the choice to test specific genes is based on weak assumptions. On the other hand, the heredibility index suggested from the twin studies implies that the environment affects the geometrical dimensions of the proximal femur. Studies (71;108;119;133;199;200) indicate that several environmental factors such as dietary intake of folate or vitamin-D influence attainment of peak bone mass and and bone loss (119;133) (71), Also, physical activity before the adolescent appears to affect peak bone mass (108;200). It therefore appears that future studies should take in to account the impact of environmental factors on hip geometry

Mechanical testing of bone tissue in vitro often requires storage of specimens for practical reasons. We had no access to freshly harvested specimens but had to rely on bones stored at -20^{o} C for up to 10 years. The process of freezing does not appear to affect the structural parameters of human bone (201). Moreover, defrosting and freezing are possible without affecting the mechanical properties of both the trabecular and cortical bone, as long as maintenance of moisture content is secured. Storage at -20^{o} C for up to one year does not seem to affect the mechanical properties significantly (201). Our load results though are identical with other cadaver studies testing frozen cadaver femurs (34;38;181). Alternatjvely, specimens may be fixed using ethyl alcohol, and formalin. As quoted by Cowin.(201), however, a number of studies have demonstrated that maximal strength do not differ significantly comparing fresh, frozen and formalin fixated specimens (38;175;181).

In study-III, we chose to test the cadaver bones with as many constants as possible to increase statistical power of the analysis regarding which of the variables that affect the maximal strength. We used a speed controlled test and a setup (figure 8)

simulating a sideways fall to obtain results being comparable to the most frequent situation resulting in fracture of the proximal femur. Other studies (176-179;181;184;202) also examined cadaverbones in a sideways fall. However there is no consistency in the literature about the speed of testing. Some studies (176-179;202) have simulated the force of gravity at impact during a fall using a loading speed of approximately 6-14 mm/s. Other studies (181;184) used a slower loading rate (0.21- 0.5 mm/sec) in their setups.

In vivo thickness of the trochanteric soft tissue absorbs some of the energy during impact in a fall. In our study, no information on soft tissue was available. We found that BMI was negatively but not significantly correlated with maximal strength. Bouxsein *et al.* (181) showed that women with hip fractures had decreased trochanteric soft tissue thickness compared to controls and tended to have lower BMI. A recent meta-analysis confirms that low BMI is a risk factor for hip fracture after adjustment for femoral BMD (203).

We performed the mechanical testing with specimens in a position similar to that suggested by Courtney *et al.* (204) to be effective during a sideways fall. The position of femur during falls, however, may vary and could result in a loading pattern of bending in contrast to our set-up resulting in both bending and compression. In theory, such difference could explain the discrepancy between *in vivo* and *in vitro* studies. Indeed, investigation of the effect of different loading angles would be of great interest in future studies. Again, the minimal access to human test material will make these studies almost impossible, however, theoretical assumptions using FE will explain some of it (34;171;205;206). In study-III we fixated the specimens with screws into the femoral shaft to secure a stable position during testing. Despite this, small movements of he specimens were impossible to avoid because of the nature of the bone with cartilage and remaining

soft tissue. This introduced some noise in the results but again cannot readily explain the discrepancy between *in vivo* and *in vitro* studies.

Several clinical studies have demonstrated that FNAL in individuals with normal body proportions are directly related with the risk of hip fracture independently of BMD (52;207;208). The fracture risk is increased with *longer* FNAL (55;56). Indeed, each centimetre increase in FNAL increases the risk of hip fracture by 50% to 80% in elderly white women (21;56). Similarly, case-control studies have demonstrated that the relative risk for hip fracture increases by a factor of 1.3 (1.2 to 1.59) for each SD increase in FNAL (54).

We tested the theoretical findings in study-IV. We included patients suffered HF consecutively during 2 years eliminating seasonal bias. The patients were older than the controls, however, the possibility to include an age-matched healthy control-group was judged almost impossible. Our approach using a sub-group analysis as well as correcting for multiple confounders in the logistic regression analysis, however, largely compensated for the difference in age between the groups. We invited controls randomly from Danish central personal register minimizing selection bias. Other groups have used similar a design (53;185), however, the number of participants in our study was higher than most other studies (21;45;53;54;56;185;187;188).

We demonstrated that FNAL and NW of the human proximal femur were increased in patients with recent hip fracture and our results are supported by a number of other case-control-studies showing that FNAL increased (52-56;168;185;188;189), and NW also was increased (21;56;166) in fracture-cases. Some studies, however found decreased NW in fracture-cases (53;190). In this thesis we only looked at women in study-

II and IV. At the time of beginning this thesis and examine the women no other control-groups were available in men.

In study-IV we found OR=1.06 (1.00-1.12) p=0.06 for FNAL to discriminate HF. The fracture risk is in other studies found with similar OR (21;53;54;56;185;188), however OR is also found to be higher (2.2) (55).

Our choice of geometrical parameters was determined after review of the literature and the software available. FNAL is widely used and examined in the literature. Also, NSA and NW have been investigated previously, while HD is the parameter less examined. Our participants in study-I, II, and III were scanned on older models of DXA-scanners. Implementing the newer strength analysis parameters in these studies was not possible.

In fact the in vitro tests on cadaver bones have revealed new engineering and mathematical assumptions. Already in 1990 Beck *et al.* (49) showed high correlation between the engineering assumptions like cross-sectional moment of inertia and cross-sectional areas and the strength. The hip strength analysis also included other geometrical parameters and engineering models like cortical thickness, buckling ratio, and section modulus enrolled in the literature. Beck showed better agreement with HSA predicted strength than femoral neck bone mineral density tested on cadaver-bones. This is also found in other studies by other authors (45;54;209) however it also is questioned (210). Hip strength or structural analysis is widely available because of its incorporation with dual energy X-ray absorptiometry and has been extensively used in clinical research. None of these new approaches has been shown to be superior to the measurement of BMD in the prediction of fracture risk (170).

The mathematical approaches also enrolled finite element analysis of the proximal femur. Keyak *et al.* (171) described this analysis method obtained from CT-scans of the proximal femur. Using FE models and other parameters obtained from CT-scans shows good correlations in predicting the strength of the proximal femur (33;34;180;184;211;212). Cody *et al.* (34) showed in a cadaver study that FE explained at least 20% more of the variance in strength than DXA. The model however is dependable of CT-scans and is not yet available in the clinic.

12 Conclusions

The first hypothesis was that the geometrical parameters of the hip were independent of sex, age, body height, body weight, menarche age, and age at menopause. In study-I we **rejected** this hypothesis. We found that body height correlated significantly with FNAL, NW, and HD in both genders. Sex also significantly influenced the geometrical parameters. Age at menarche and menopause, however, only correlated with NSA.

The second hypothesis was that polymorphisms in genes known to affect BMD (*i.e.* MTHFR, $P2X_7$ and LRP5) were associated with the geometry of the proximal femur. The geometrical parameters are not associated with these genetic polymorphisms, however, our findings in study-II, led us to **rejected** this hypothesis.

The third hypothesis was that the maximal strength of the proximal femur as tested post-mortem is independent of BMD and the geometrical parameters. In study-III this hypothesis was **rejected** since we found that BMD and FNAL correlated significantly to the maximal strength. Indeed, BMD_{neck} and FNAL explained up to 62% of the maximal strength of the proximal femur tested *in vitro* in non-osteoporotic persons.

Finally the fourth hypothesis was that the geometrical parameters of the proximal hip, BMD, and the combination of these did not differ significantly between patients with hip fracture and controls. This hypothesis was **rejected** since our data showed that women with recent HF had significantly lower BMD and longer FNAL than controls. Moreover, patients with trochanteric fractures had significantly higher NW.

13 Final comments and clinical perspectives

Our data suggest that measurement of hip geometry may be employed in the work-up in patients with suspected osteoporosis in addition to conventional DXA. The conduct of a large prospective study to verify our findings would be the logical next step. Moreover, such study should test the new geometrical measurements proposed by Beck *et al.* (49) (HSA).

14 Summary in English

The thesis is comprised by a review and 4 original papers – a cross-sectional study (published) a cross-sectional genetic association study, an *in vitro* experimental study, and a case-control study (drafts to be submitted).

Risk factors for hip fracture (HF) include age, previous history of fracture and low body weight or body mass index. HF is, furthermore, one of the most serious consequences of osteoporosis. The purpose of the thesis was to investigate the potential use of measurements of the macroscopic geometry of the human proximal femur to predict the risk of HF. Moreover, we wanted to investigate the relative power of geometric parameters and bone mineral density (BMD) in that respect. Clinical studies have suggested that geometrical parameters of the hip such as femoral neck axis length (FNAL), neck-shaft angle (NSA), neck width (NW), and femoral head radius (HR) may predict the risk of HF independent of BMD. Few experimental data, however, have been published to support this. There is a significant genetic contribution to the risk of osteoporosis. Polymorphisms in a number of genes including those coding for the methylene-tetrahydrofolate reductase (MTHFR c.677C>T), the purinergic $P2X_7$ receptor, and the low-density lipoprotein-receptor-related protein 5 (LRP5 exon 9 (c.266A>G)), have been associated with an increased fracture incidence and/or reduced bone mineral density (BMD). Hip geometry, however, is independently associated with risk of HF and studies in twins have suggested that hip geometry is genetically programmed. There are, however, discrepancies in the literature. Furthermore, no studies have described the natural variation in hip geometry in relation to Danish population characteristics.

In a cross-sectional study, comprising 94 men and 155 women aged 19 to 79 years, we studied the normal variation in hip geometry. Our data confirmed that the macroscopic

geometry of the human proximal femur differs between men and women and that FNAL, NW, and HR correlate with body height. Moreover, NW is associated with age in men but not in women.

In a cross-sectional study, comprising 800 perimenopausal women aged 44 to 59 years, no significant association between four genetic polymorphisms (MTHFR c.677C>T genotype polymorphism, the $P2X_7$ A1513C polymorphism, the $P2X_7$ T1729A polymorphism, and the LRP5 exon 9 (266A/G) polymorphism) and hip geometry could be demonstrated.

In a cross-sectional study comprising 38 bone specimens excised from recently diseased patients (age 37 to 55 years) during medico-legal autopsy, we found that the *in vitro* maximal strength of the proximal femur was predicted by BMD ($R=0.49$, $p<0.01$) and FNAL ($R=0.68$, $p<0.001$).

Finally, in a case-control study comprising 162 women with recent HF and 248 healthy controls aged 51 to 98 years, we found that patients with HF had significantly lower BMD and higher FNAL than controls. Moreover, patients with trochanteric HF had significantly higher NW compared with controls.

Thus, hip geometry and extended analysis of regional BMD data can improve the prediction of strength of the proximal femur and the risk of HF. Our results support the use of measurement of hip geometry in clinical routine in addition to conventional DXA.

15 Summary in Danish

BETYDNINGEN AF KNOGLESTRUKTUR OG -GEOMETRI FOR BRUDSTYRKEN I PROXIMALE FEMUR

Afhandlingen består af en oversigt samt 4 originale studier, ét tværsnitsstudie, ét (tværsnits-) genetisk associationsstudie, ét eksperimentelt studie og ét case-kontrol-studie. Risikofaktorer for hoftebrud (HF) inkluderer alder, tidligere brud, lav vægt eller BMI. HF er endvidere en alvorlig konsekvens af osteoporose. Formålet med afhandlingen var at undersøge den mulige kliniske brug af opmålinger af den makroskopiske geometri af proksimale femur med henblik på at forbedre prædiktionen af hoftebrud (HF). Kliniske studier tyder på, at geometrien i hoften (femoral neck axis length (FNAL), neck-shaft angle (NSA), neck width (NW) og femoral head radius (HR) prædikterer HF uafhængigt af bone mineral density (BMD), men der foreligger kun få eksperimentelle studier, der understøtter dette. En række studier har vist, at genetiske faktorer har betydning for udviklingen af osteoporose. En række genetiske polymorfier i bl.a. de gener, der koder for methylene-tetrahydrofolate reductase (MTHFR c.677C>T), den purinerge $P2X_7$ receptor, og low-density lipoprotein-receptor-related protein 5 (LRP5 exon 9 (c.266A>G)), er associeret med en øget frakturincidens og/eller reduceret BMD. Tvillingestudier har endvidere påvist, at genetiske faktorer har betydning for hoftens geometri. Litteraturen er dog ikke konsistent. Endelig foreligger der ingen studier der har beskrevet hoftegeometrien i den danske befolkning.

I et cross-sectional studie omhandlende 94 mænd og 155 kvinder (alder 19-79 år) undersøgte vi normalvariationen i hoftegeometrien. Vore data bekræfter at den makroskopiske geometri af den humane proksimale femur er forskellig i raske danske

mænd og kvinder samt at FNAL, NW og HR afhænger af vægten. Derudover er NW associeret med alder hos mænd.

I et cross-sectional studie omhandlende 800 perimenopausale kvinder (alder 44 til 59 år) fandt vi ingen signifikant association mellem de fire genetiske polymorfier og geometrien.

I et cross-sectional studie omhandlende 38 cadaver-hofteknogler fra nyligt afdøde patienter (alder 37 til 55 år) fandt vi, at in vitro maksimal styrke af proksimale femur før HF kan prædikteres af BMD ($R=0.49$, $p<0.01$) og FNAL ($R=0.68$, $p<0.001$).

Endelig, i et case-control studie omhandlende 162 kvinder med nylig HF og 248 raske kontroller (alder 51 til 98 år) fandt vi significant lavere BMD og længere FNAL. Derudover har patienter med trochanter HF signifikant bredere NW sammenlignet med kontroller.

Hofte geometri og udvidede analyser af regional BMD kan øge og styrke prædiktionen af styrken samt prædiktionen af risikoen for HF. Vore resultater støtter brugen af hofte geometri i den daglige klinik som supplement til DXA-scanning.

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