Distal radius fracture in men from working age to the oldest. Bone mass and patient-related outcome.

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Lisa Egund

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UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle Distal radius fracture in men from working age to the oldest Bone mass and patient-related outcome

Abstract

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Recruitment was as follows: men who fractured during 1999-2000 were evaluated retrospectively in 2003 and men who fractured during 2003-2007 were followed prospectively for one-year post-fracture. A total of 233 patients, response rate 40%, were enrolled and compared with 643 controls. Fractures from all degrees of trauma were included.

In paper I, we asked if bone mineral density (BMD) differed between men with distal radius fracture and a control group representative of the background population. Already from the age of 40, men with a distal radius fracture had lower BMD, the difference becoming more pronounced with increasing age. BMD did not differ with trauma level. Osteoporosis was more prevalent at all ages (20-39y: 8.5% vs 1.5%; 40-64y: 16.8% vs 5.1%; >65y: 23.3% vs 8.3%).

Sex hormones are crucial to skeletal health in adolescence and older age. In paper II, we investigated the sex hormone profile in younger men with distal radius fracture in order to elucidate, if this contributes to explaining the low bone density and osteoporosis previously observed. The main finding was that younger men, aged 20 to 50, have an altered hormone profile with reduced levels of both free estradiol and testosterone and elevated luteinizing hormone when compared to age-matched controls. A distal radius fracture and probably other appendicular fractures in younger men might therefor be early signs of silent hypogonadism for clinicians to be aware of.

Self-reported outcome after distal radius fracture differ between young and elderly. In paper III, we asked how self-reported outcome relate to fracture appearance, BMD and fracture risk in young and elderly men. We found that men over the age of 65 are more likely to have displaced fractures at both initial presentation and at follow up and higher degree of disability independent of radiographic appearance at follow up. BMD per se was not related to displacement or disability; however, most older men initially presenting with a displaced fracture also had unacceptable reduction at follow-up and higher future fracture risk, indicative of poorer bone quality.

Sick leave following a fracture is a common negative consequence. But what factors are of importance after distal radius fracture and what is the impact of patient- and fracture related factors, respectively, on length of sick leave? In paper IV we found that higher self-perceived disability and pain as early as one week after fracture are the strongest predictors of length of sick leave, regardless of treatment type.

In conclusion, our results show that in men, as in women, a distal radius fracture is a red flag for impaired bone strength. Men should be evaluated for osteoporosis as routine and sex hormones should also be considered. The treatment of older men with radius fracture needs further improvement, since many have disability 1 year after fracture. High degree of pain early after fracture is the greatest risk factor of longer sick leave.

Key words: Distal radius fracture, men, BMD, outcome, sex hormones, sick leave

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To the men of my life, Jack and Max

"The best things in life make you sweaty."

Edgar Allan Poe

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List of papers

This thesis is based on the following papers:

I. High prevalence of osteoporosis in men with distal radius fracture – a cross-sectional study of 233 men
L Egund, F Mcguigan, K Önnby, A Givercman, K Åkesson
Calcified Tissue International 99: 250-258, 2016
doi: 10.1007/s00223-016-0142-6

II. Low estradiol and testosterone and high luteinizing hormone in younger men with distal radius fracture
L Egund, S Isaksson, F Mcguigan, A Givercman, K Åkesson
Submitted

III. Patient-related Outcome, Fracture Displacement and Bone Mineral Density following distal radius fracture in Young and Older Men
L Egund, F Mcguigan, K Önnby, N Egund, J Besjakov, K Åkesson
Submitted

IV. Disability and pain are the best predictors of sick leave after a distal radius fracture in men
L Egund, F Mcguigan, K Önnby, A Givercman, K Åkesson
Journal of Occupational Rehabilitation. 2020 Feb 12
doi: 10.1007/s10926-020-09880-4

Abbreviations and definitions

AO	Arbeitsgemeinshaft für Osteosynthesefragen. The classification of fractures: Type A are extra-articular, type B partial articular and type C complete articular.
Barton´s fracture	An intra-articular fracture of the distal radius with dislocation of the radiocarpal joint. There are two types of Barton's fracture – dorsal and volar, the latter being more common.
BMD	Bone mineral density (g/cm^2)
BMI	Body mass index (kg/m^2)
CCI	Charlson comorbidity index
cFT	Calculated free testosterone
Colle´s fracture	An extra-articular fracture of the distal radius with dorsal angulation and impaction.
DASH	Disabilities of the Arm Shoulder and Hand: a patient reported outcome instrument that measures disability of the upper extremity
DXA	Dual x-ray absorptiometry
E2	Estradiol
FRAX	Fracture Risk Assessment Tool
Hypogonadism	Hypogonadism in men is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary testicular axis
IOF	International Osteoporosis Foundation
LH	Luteinizing hormone
MCS	Mental Component Scale SF-36
MOF	Major Osteoporotic Fracture (hip, wrist, humerus and clinical spine)
Osteoporosis	A systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue leading to increased fragility and susceptibility to fracture. Diagnostic criterion for osteoporosis is a T-score below -2.5. Low bone density or osteopenia is defined as a T-score between -1 and -2.5 and normal BMD as a T-score above -1.
PCS	Physical Component Scale SF-36
PROM	Patient Reported Outcome Measurement
ROM	Range of motion
SF-36	Short Form 36 is a patient-reported outcome instrument that measures physical and mental health.
SHBG	Sex hormone binding globulin
Smith´s fracture	A fracture of the distal radius with associated volar angulation of the distal fracture fragment. Classically, these fractures are extra-articular transverse fractures and can be thought of as a reverse Colle´s fracture.
T	Testosterone
WHO	World Health Organisation

Abstract

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Populärvetenskaplig sammanfattning

Osteoporos är ett stort folkhälsoproblem. Denna, ofta tysta sjukdom, orsakar ett stort lidande för de drabbade individerna och samhällskostnaderna är väldigt höga och dessutom kraftigt stigande med den åldrande befolkningen. Osteoporos har genom många år trots vara en ”kvinnosjukdom”. Männen har ansetts vara skyddade, då de inte går igenom klimakteriet med fallande östrogenproduktion, så som kvinnor gör. Problemet är, att också äldre män bryter handleder och höfter och ett ännu större problem är, att många av dessa män varken utreds eller behandlas för osteoporos.

Forskning av kvinnor från 40 års ålder har tydligt visat, att en bruten handled ofta är det första symptomet på osteoporos. Tyvärr har forskningen fokuserat nästan enbart på kvinnor och det fanns väldigt begränsad kunskap om hur det såg ut hos män med brutna handleder. I studier om patientupplevd funktion efter handledsfraktur har män utgjort en mindre andel, varför vetskapen om hur det går för speciellt de äldre männen är svag.

Vi genomförde därför en forskningsstudie av män med handledsfrakturer och denna avhandling baseras på fyra studier, där vi har undersökt benmassa, patientupplevd funktion ett år efter skada samt vilka faktorer som är viktiga för sjukskrivningslängd efter en bruten handled. Totalt 233 män med handledsfraktur i åldern 20-88 år deltog i studien och de jämfördes med jämnåriga män (kontroller).

Vi såg, att totalt sett 17 % av männen med handledsfraktur hade så låg benmassa, att de hade diagnosen osteoporos, vilket var 3 gånger fler än hos kontrollerna. Hos män mellan 65-88 år hade 25% osteoporos och hos de lite yngre 40-64, 17%. Vi såg inte några olikheter i annan sjuklighet mellan män med handledsfrakturer och kontroller, som kunde förklara denna skillnad. Det mest intressanta var att till och med hos de helt unga mellan 20-39 år fanns en tendens till lägre bentäthet.

Vi undersökte därför halterna av könshormoner hos de yngre med fraktur och jämförde med jämnåriga kontroller. Män med handledsfraktur hade klart lägre halter av både östrogen och testosteron. Speciellt östrogen är väldigt viktig för att bygga upp och bibehålla benmassan genom livet också hos män, varför vi tror att de lägre nivåerna av könshormoner redan i ung ålder kan vara en bidragande orsak till den ökade förekomsten av osteoporos hos män med handledsfraktur.

Äldre män från 65 år och uppåt med handledsfraktur upplevde en sämre funktion ett år efter skada jämfört med de yngre. Trots behandling var deras frakturer oftare felställda. Detta tyder på att åldersrelaterad försämrad benkvalitet och hållfasthet har

betydelse, vilket speciellt sågs hos de som hade en felställd fraktur när de kom till akuten.

Handens funktion är central i de allra flesta göromål och därmed också i arbetet. Vi såg att en fjärdedel av män med handledsfraktur inte behövde vara sjukskrivna medan några få inte har återgått till arbete efter ett år. Mest intressant var, att de som hade väldigt ont en vecka efter frakturtillfället hade större risk för längre sjukskrivning. Detta var oberoende om de hade blivit opererad eller inte. Det visar, att om vi kan hjälpa dessa individer med att hantera och minska smärtan, så kommer de sannolikt kunna återgå till arbete snabbare.

Sammanfattningsvis kan vi konstatera att också män med handledsfraktur har en ökad risk för låg bentäthet och osteoporos. Sjukvården fokuserar mer och mer på att med kost och motionsråd förebygga sjukdomen samt att tidigt hitta de som är i riskzonen. Män finns också i denna riskzon. Det behövs mer forskning för hur vi bäst behandlar äldre män med handledsfraktur för att minska andelen med dålig självupplevd funktion. Dessutom är sjukvården i behov av strategier för rehabilitering efter handledsfraktur för att minska risken för långvarigt lidande och sjukfrånvaro.

Introduction

The human skeleton developed to be both lightweight and yet strong enough to withstand large forces. However, with increasing age or illness, the bones weaken and become more susceptible to fractures. With the rapidly increasing longevity which surpasses the evolutionary adaptions of the skeleton, it is not surprising that fragility fractures are exploding in numbers.

Evolution has granted men with a stronger skeleton. Men still have fractures and yet, they are overlooked in regard to studying the earliest sign of an overall impaired bone strength, a fracture to the distal radius. So, this book is all about men.

The skeleton

The term skeleton comes from Greek σκελετός (skeletós), which means 'dried up'. In contrast to this somewhat bleak word of origin, the skeleton is a living, constantly changing tissue. It has several vital functions. It acts as a scaffold to anchor muscles and protect organs including the brain, heart and spinal cord. It also serves as storage for the hematopoietic bone marrow and several minerals such as calcium and phosphate. During the last decade it has become evident that the skeleton has a crucial role as an endocrine regulator of glucose homeostasis [(1)]. It is a very dynamic environment that can respond to increasing load and is able to self-repair after fracture.

Structure

Bone is typically made up of a strong and dense outer surface, the cortical bone, and a honeycomb-like three-dimensional porous internal structure, the trabecular bone, leaving place for the bone marrow, figure 1. Both cortex and trabeculae are composed of extra-cellular matrix and bone cells.

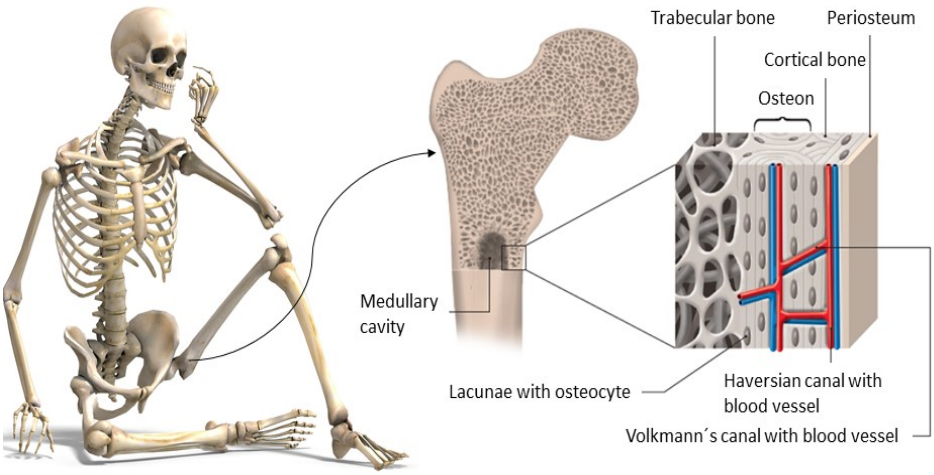


Figure 1. The human skeleton and its main bone structure

Three main types of cells are present in bone tissue, figure 2 [(2)]. *Osteoblasts* are the bone cells responsible for forming new bone, which are derived from the mesenchymal stem cells of bone, the osteoprogenitor cell. Osteoblasts are mainly found in the outer and inner lining of bone, the periosteum and endosteum. Osteoblasts synthesize the organic components of the bone matrix (osteoid) consisting of type I collagen, glycosaminoglycans and proteoglycans. The secreted matrix surrounding the osteoblast calcifies as crystals of calcium and inorganic phosphate deposit on the scaffold made by layers of collagen fibrils.

The osteoblast then differentiates to a lining cell, undergoes apoptosis or becomes trapped within the matrix and by doing so, it changes structure and now becomes an *osteocyte*. Osteocytes maintain the mineral concentration of the matrix via the secretion of enzymes. Each osteocyte lies in a space called lacuna and adjacent osteocytes communicate with each other via long cytoplasmic processes that lie in narrow channels within the matrix, canaliculi. Through these connections, called gap junctions, the osteocytes communicate through a variety of systemic and locally generated signals (physical load and strain in particular), translating them into biological signals. These signals are transmitted to other osteocytes but also to osteoblasts at specific locations to induce bone formation where necessary [(3)]. Osteocytes also communicate with the *osteoclasts*, the cells responsible for bone resorption, which are found on the surfaces of bone. They are multinucleated cells that originate from the hematopoietic cell lines as other phagocytic cells such as the macrophage.

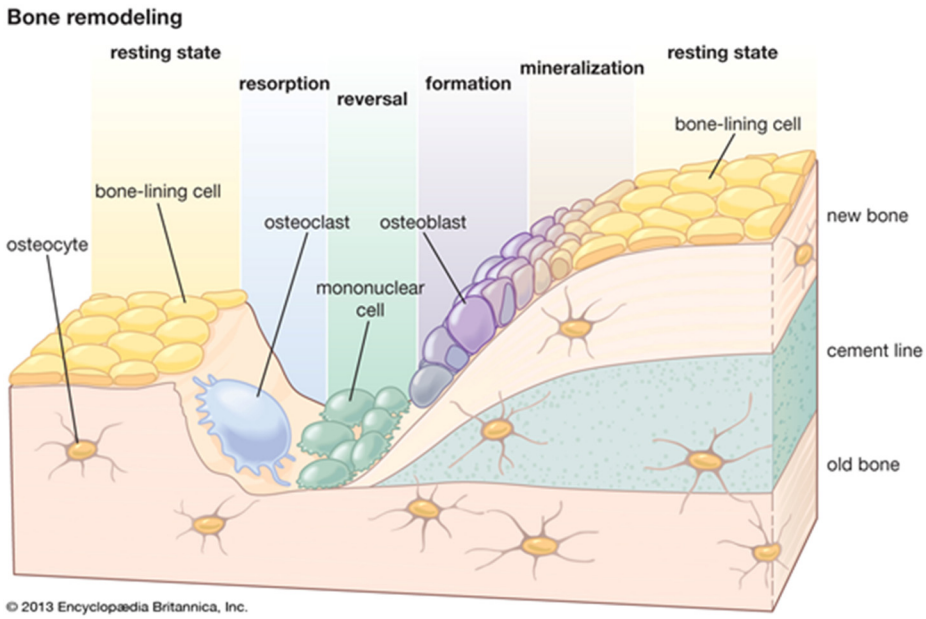


Figure 2. The bone remodelling cycle. From Encyclopædia Britannica. https://www.britannica.com/science/bone-remodeling

Bone metabolism

The dynamic nature of bone means that new tissue is constantly formed, and old, injured, or unnecessary bone is dissolved for skeletal repair or for calcium release. Calcium is critical for mediating vascular contraction and vasodilatation, muscle function, nerve transmission, intracellular signalling and hormonal secretion. Bone serves as the major storage site for calcium and its metabolism is largely regulated by parathyroid hormone (PTH) and vitamin D [(4)].

The regulation of bone metabolism is orchestrated by the intricate relationship between osteoclasts, osteoblasts and an array of hormonal and regulatory stimuli.

The relative levels of these local and systemic factors dictate whether healthy, balanced bone metabolism ensues (table 1 and 2).

Table 1. Factors regulating bone resorption

Stimulation	Inhibition
Parathyroid hormone (PTH)	Calcitonin
Cortisol	Sex hormones
Thyroid hormone	Transforming growth factor β (TGF-β)
Prostaglandin (PGE2)	Osteoprotegerin (OPG)
Interleukins 1 and 6	Interleukin 4, 10, 13 and 18
Macrophage colony stimulating factor 1 (CSF-1)	Interferon γ
Tumor necrosis factor α (TNF-α)	
Rank Ligand (RANKL)	
1,25 Dihydroxyvitamin D3	

Table 2. Factors regulating bone formation

Stimulation	Inhibition
Growth hormone (GH)	Serotonin (intestinal)
Parathyroid hormone (PTH)	Cortisol
Prostaglandin (PGE2)	Interferon γ
Serotonin (cerebral)	Tumor necrosis factor α (TNF-α)
Transforming growth factor β (TGF-β)	Interleukins 1β and 7
Insulin-like growth factor (IGF-1)	Sclerostin
Fibroblast growth factors (FGF-2)	1,25 Dihydroxyvitamin D3
1,25 Dihydroxyvitamin D3	
Leptin	

Bone during the life-course

The skeleton grows relatively slowly during childhood and there is no difference in bone mass between the genders before puberty. Puberty kick-starts a growth spurt and bone mass more than doubles in skeletal sites such as the spine and femoral neck [(5)]. Males enter this skeletal growth spurt approximately 2 years later than females, have a longer growth period and grow faster [(6)].

Around the third decade the individual reaches peak bone mass, the maximum amount of bone accrued during young adulthood after completion of growth, see figure 3. The exact age differs at different skeletal sites; it occurs as early as 17 and 18 years in the hip and as late as 35 years in other locations as the distal radius [(7–9)]. About 60-80% of peak bone mass is explained by heritable factors and hence 20-40% can be modified by environmental factors and lifestyle choices. Especially, physical activity and an adequate calcium intake during late childhood have shown to have a large impact on peak bone mass [(10)]. In young men, levels of sex hormones are of importance on bone mineral density and bone micro-architecture [(11)].

In the years following the attainment of peak bone mass, bone formation and resorption are at first in balance but then resorption becomes greater resulting in a bone loss

between 0.5-2% per year [12,13]. Up to the age of 65, about half of the variation in bone mass can be explained by peak bone mass acquired earlier in adult life [14], which illustrates the importance of acquiring the greatest bone mass possible to prevent future fragility fractures.

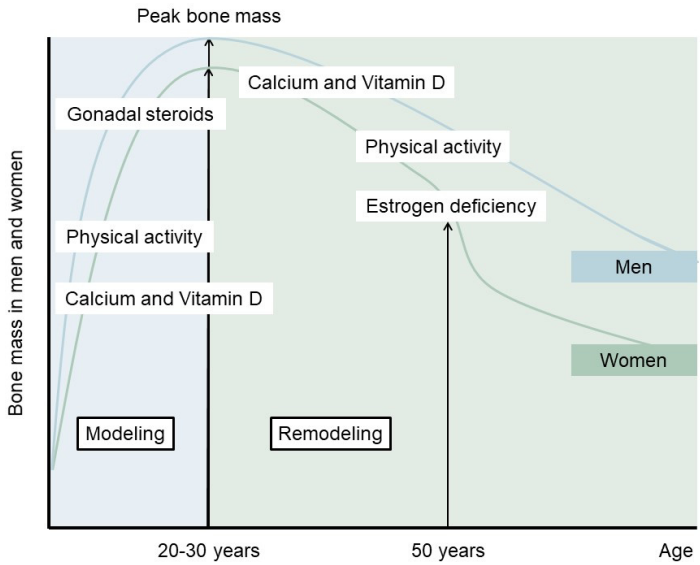


Figure 3. Bone mass through out life in men and women and factors of importance in the modelling and remodelling phases

Determinants of bone strength

Bone strength is the maximal amount of load tolerated before structural failure occurs [15] and with increasing load or strain, micro-cracks develop, propagates and eventually leads to a complete fracture [16].

Bone mass is one aspect of bone strength, but how this mass is distributed, the bone structural properties, is of major importance. Bone geometry addresses the diameter of the bone and the cortical thickness. The two schematic bones in figure 4a (one small and thick and the other wide and thin) have the same cortical area; however, the one with larger diameter have its mass distributed further away from the bending axis, resulting in an increased moment of inertia and thereby increased resistance to bending/fracture. The micro-architecture involves the thickness and connectivity of the trabeculae and also the cortical porosity, the fraction of void volume within the bone. The cortical and trabecular microarchitecture have been shown to play a critical role to the mechanical properties of bone [15,17–20]. Figure 4b illustrates the importance of the

trabeculae to bone strength. The distal radius fractures is an excellent example of the importance of bone properties as the fractures involve the metaphysis, an area with lesser cortical thickness and larger amount of trabecular bone.

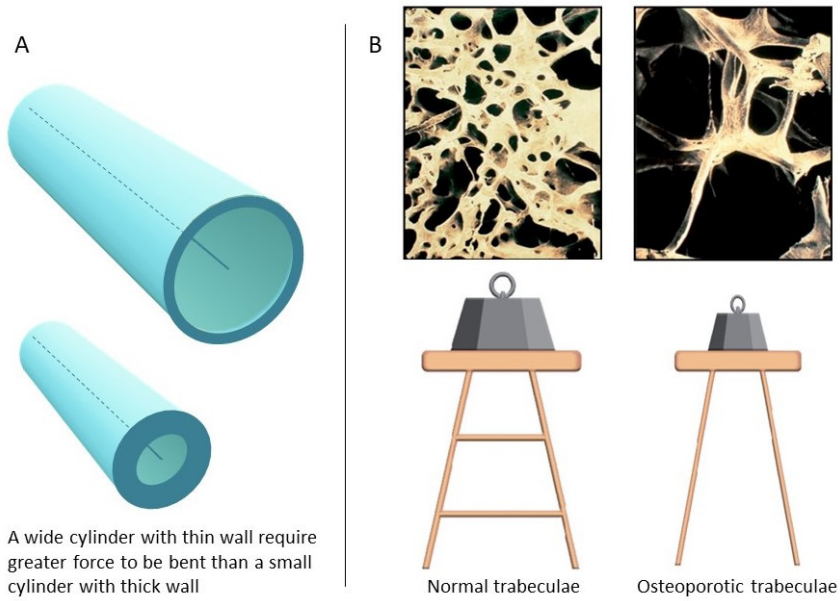


Figure 4. Schematic illustration of the importance of whole bone geometry and micro-architecture to bone strength. In part adapted from Microarchitecture, the key to bone quality, Maria Luisa Brandi, Rheumatology, Volume 48, October 2009.

Bone structural properties, including tissue properties, are being extensively studied in their importance to bone strength, risk of fracture and in targeting treatment for osteoporosis. They can be viewed in a hierarchical fashion from nano- to macroscopic levels; failure at one level affects the total resilience to fracture at the other levels [21] (figure 5).

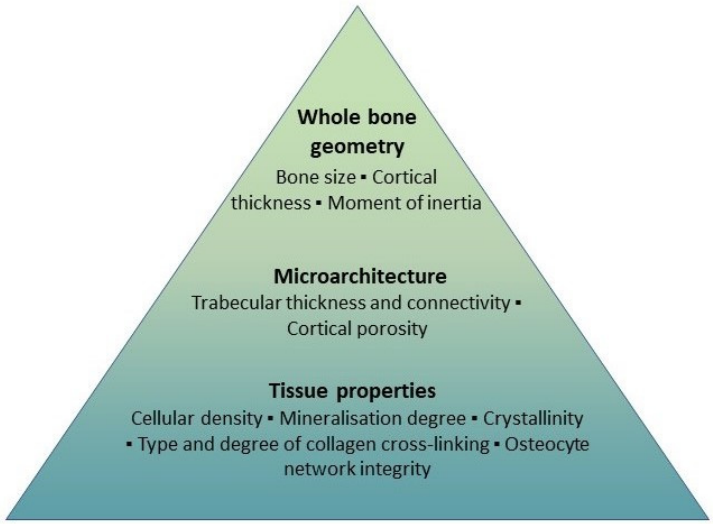


Figure 5. The several traits influencing bone strength are schematically in the figure. The base of the pyramid represents the the smallest components that form bony tissue, which comprise amount and biophysical properties of the organic or the inorganic components. The centre of the pyramid shows the micro-architectural properties- the way bony tissue is spatially organized in the trabecular and cortical components. Finally, in the top of the pyramid are the macroscopical traits that define whole bone geometry. Adapted in part from Fonseca et al 2014 [(22)].

Gender differences in skeletal structure

Men are on average 10% taller than women because of greater bone length. They have a 25-30% larger cross-sectional bone area at both central (spine) and peripheral sites (distal tibia, radius) even after correction for bone length. The greater bone width in men is a result of greater periosteal expansion during adolescence, whereas women increase their cortical thickness by limiting the endocortical expansion, see figure 6 [(23)].

At the age of peak bone mass, the cortical thickness is similar between sexes. Males have a marginally lower cortical volumetric bone mineral density (vBMD) mostly due to a higher cortical porosity [(24)], but a 26% greater trabecular vBMD due to thicker, more plate-like trabeculae. There is no difference in trabecular number and separation between men and women [(25)].

Overall, men have wider bones with thicker trabeculae and thus greater bone strength.

During adult life there is a continuous general expansion in bone width, of approximately 15%, by means of periosteal apposition [(28)]. However, a simultaneous endocortical expansion of 25-40% results in a thinner cortex. This medullary expansion and cortical thinning are much greater in women compared to men [(26,29)].

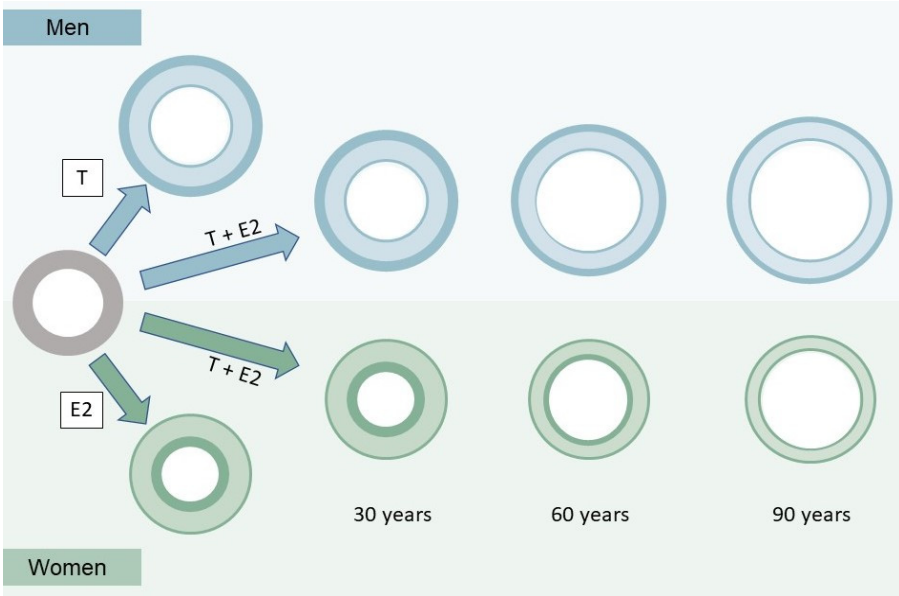


Figure 6. Cross-section of a long bone illustrating differences in bone geometry between the sexes during life. Schematic presentation of the role of estradiol (E2) and testosterone (T) on bone geometry according to gender. In men, the combined action of both T and E 2 lead to greater bone size due to greater periostal apposition. The prevailing effect of E 2 results in higher endosteal bone formation in women. Bone loss during aging occurs in a different fashion between men and women. Women lose more bone on the endosteal surface and in the trabecular portion of bone, while men lose mainly bone mass in the cortical bone. Modified in part from figures published in [26,27].

Trabecular thinning starts early in adult life, already after the age of 20, and trabecular bone loss accounts for approximately 1/3 to 1/2 of the total bone loss. Women mainly loose trabeculae while in men, trabeculae undergo thinning [25].

In summary, men undergo a continuous deterioration of bone micro-architecture with age, but due to the absence of an "androgen-pause" combined with the wider bones and thicker trabeculae at the age of peak bone mass, they are at lower risk of fragility fractures compared to women.

Sex hormones

The differences in skeletal properties between men and women are mainly driven by differences in sex hormones, testosterone and estradiol.

Testosterone is the dominant gonadal androgen in men. The majority, around 90%, is produced by the Leydig cells in the testes, but the adrenal glands and other peripheral tissues add a minor contribution. Estradiol, the main hormone of the estrogen family, is also produced in the testes but most (80%) is derived through conversion of

testosterone by the enzyme aromatase (CYP19A1). Aromatase is found in almost all peripheral tissues with the by far highest concentrations in adipose tissue.

The amount of testosterone synthesized, and thus also the amount of estradiol, is regulated by the hypothalamic–pituitary–testicular axis as illustrated in figure 7. When testosterone levels are low, gonadotropin-releasing hormone (GnRH) is released by the hypothalamus, which in turn stimulates the pituitary gland to release follicle stimulating hormone (FSH) and luteinizing hormone (LH). LH acts on the Leydig cells in the testes to produce testosterone.

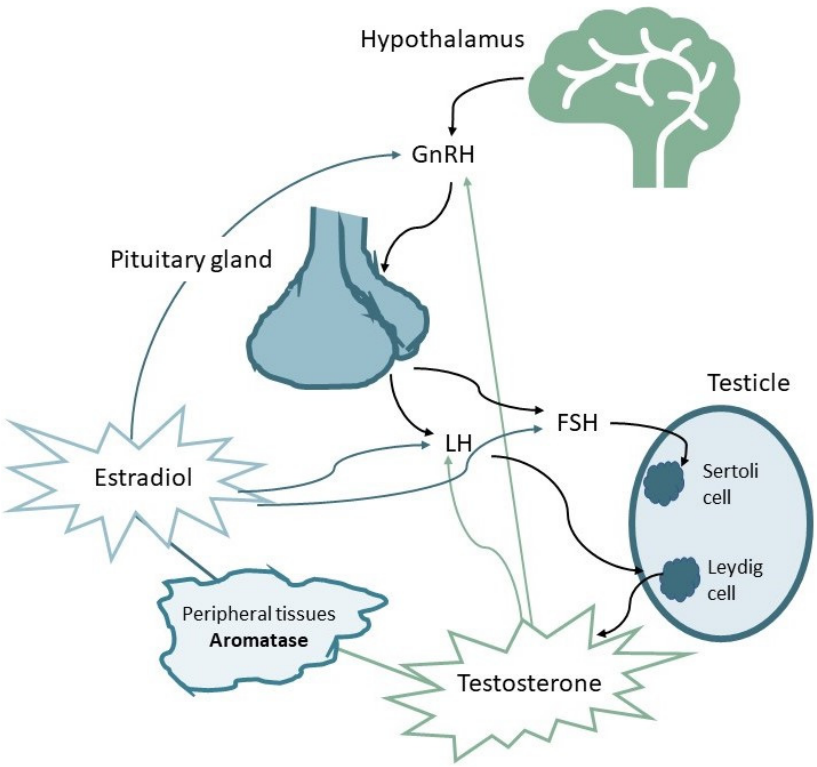


Figure 7. The hypothalamic–pituitary–gonadal axis

Only a small portion of the total circulating testosterone and estradiol is in the free form and this is the biological active fraction. The circulating sex hormone binding globulin (SHBG) binds approximately 65% and most of the remaining hormones are bound to albumin and other proteins.

Testosterone and estradiol exert their action by binding to estrogen- and androgen receptors, respectively. Due to the hydrophobic nature of steroids, they diffuse across the plasma membrane of the cells. Estrogen- and androgen receptors are present both in the cell membrane, mitochondria and nucleus and binding of the corresponding hormone initiates a cascade of intracellular signalling [30] with various effects depending on the targeted tissue.

Throughout adult life, the total concentration of sex hormones decreases only marginally in men. However, SHBG increases with age which results in a lower free fraction of testosterone and estradiol [31]. Men experience rather small declines of testosterone production with age, and thus have sufficient substrate for conversion to estradiol, which means that older men generally have higher levels of estradiol than postmenopausal women,; this might be a plausible explanation for the better conservation of the male skeleton [32].

The effects of sex hormones on the skeleton

The effects testosterone and estradiol exert on the male skeleton differ during growth and in adult life.

The growing skeleton

Levels of sex hormones are very low in childhood. In boys, with the onset of puberty both testosterone and estradiol begin to increase simultaneously. Both sex hormones stimulate the growth plates of long bones and the longitudinal growth spurt begins [33,34]. As puberty goes on, the continuous rise in levels of testosterone ensures a corresponding rise in estradiol. By late puberty, estradiol levels reach a threshold and by passing this level, its action shifts from stimulation and now instead inhibits the growth plate and induces its closure [34]. Estradiol increases bone mass mainly by increasing BMD, especially of cortical bone, whereas testosterone increases the size of the bone by means of a higher mechanical load exerted on the bone by increasing muscle mass [35]. In young men, twenty years of age, free testosterone has been found to be a positive predictor of cortical bone size and free estradiol independently predicts cortical volumetric BMD [11]. Estradiol is also associated with the increase in BMD seen in young men up to the age of 39 [36].

Combing the facts, that boys enter puberty approximately 2 years later than girls giving them a longer growth period before puberty, and they also grow faster during puberty, results in the advantageous bone properties seen in men.

The older skeleton

During adult life and ageing, estradiol has been shown to be most important of the sex hormones in maintenance of skeletal health in both sexes. This was demonstrated in a study of older men where endogenous estradiol and testosterone were blocked and subsequently administered exogenously [37]. The study revealed that, following androgen blockage, estradiol alone was almost completely able to prevent an increase in bone resorption whereas testosterone alone was much less effective. In men from the age of sixty, estrogen deficiency causes a decrease of both trabecular and cortical bone [38–40]. In older men, low estradiol rather than testosterone, is associated with low bone mineral density and accelerated bone loss [36,41]. Testosterone, on the other hand, has not shown to have the same independent effect, but probably affects bone indirectly via estradiol and by its effect on lean mass.

Levels of sex hormones are also correlated to *fracture risk*. Having low estradiol and high SHBG is a significant risk factor of fracture, which only partially is explained by the effect on bone density [42,43]. Estradiol, in contrast to testosterone, has been shown to have a causal effect on fracture risk in a study using a mendelian randomization approach [44]. The findings are not universal, as others have found testosterone to be a stronger predictor of future fragility fractures than estradiol [45].

In conclusion, in men, both testosterone and estradiol are crucial for skeletal growth and in attaining peak bone mass, but estradiol appears to be of most importance in maintaining skeletal health late in life. However, there is a gap in knowledge as information is limited on the sex hormone profile on young and middle-aged men with fracture.

Osteoporosis and fragility fractures

Osteoporosis is defined as "a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue leading to increased fragility and susceptibility to fracture" [46]. It affects an estimated 75 million people, men and women, in Europe, USA and Japan [47] and in Sweden half a million individuals above the age of 50 have osteoporosis [48].

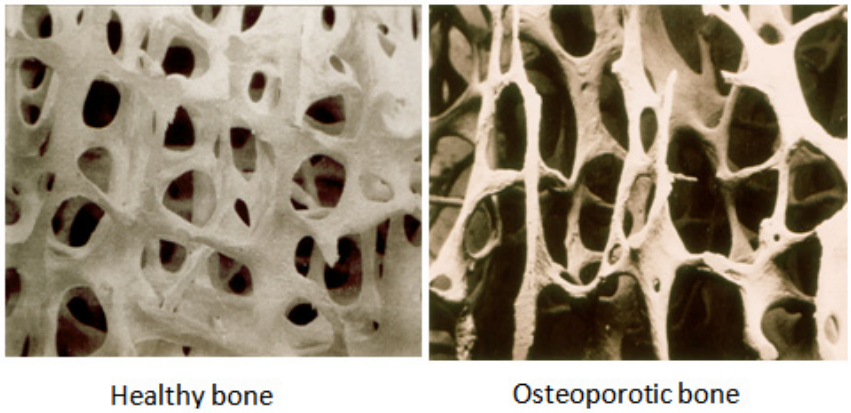


Figure 8. Picture illustrating the major differences in trabeculae of healthy and osteoporotic bone. Healthy bone have thick trabeculae with high connectivity. The osteoporotic bone exibit thinning and loss of trabeculae.

Osteoporosis is often called a "silent disease" because it progresses without symptoms until a fracture occurs. Fractures are the primary clinical consequence of osteoporosis. Fragility fracture are fractures that result from mechanical forces that would not ordinarily result in fracture i.e. caused by low energy trauma, which is a fall from standing height or less [(49)]. The most common fragility fractures are those of the hip, pelvis, vertebrae, humerus and wrist[(50)] and in long bones, they are most often located at the metaphysis. Those involving the hip and vertebrae are associated with the greatest morbidity and mortality as well as health care expenditure.

It is estimated that 9 million new fragility fractures occur worldwide [(51)]. The incidence of new fragility fractures in Sweden is about 120,000 annually, which is estimated to increase by 27% by the end of 2030 [(48)]. Osteoporosis and the related fractures not only cause individual suffering, the annual socioeconomic costs are estimated at 3.5 billion kronor.

Osteoporosis in men

Osteoporosis has been considered a women's issue for many years, but men are not spared despite their better skeletal properties. In Europe, 1.2 million fragility fractures were estimated to have occurred in men in 2010 [(51)]. One fifth of all those with osteoporosis in Sweden are men, and for Swedish men above the age of fifty, 29% will experience at least one fragility fracture [(48)].

Although fewer men develop osteoporosis, the consequences for them are often more severe, since their general health is often very poor when they present with a fragility fracture. For men, suffering a hip fracture is associated with greater morbidity and

mortality when compared to women [52,53]; men are twice as likely to die in hospital after a hip fracture [54]. Despite this fact, men are often not evaluated for osteoporosis when presenting with a low energy fracture and even fewer receive treatment [55,56].

Osteoporosis in men *is* a common problem, just as it is for women. In the light of the growing aging population and the improving longevity, osteoporosis in men will become an even greater challenge to society and health care systems.

Pathophysiology

Osteoporosis is a heterogeneous entity with multiple underlying causes. It can be separated into primary (age-related or idiopathic) and secondary osteoporosis, see table 2. Secondary osteoporosis is a result of underlying diseases, medications or lifestyle factors and may account up to 40% of the cases of osteoporosis in men [57]. Several factors may be present in the same individual. The three major causes of secondary osteoporosis in men are glucocorticoid excess (either endogenous or, more commonly, chronic glucocorticoid therapy), alcohol abuse and hypogonadism (low testosterone).

Table 2. Common causes of osteoporosis in men

Primary osteoporosis	Age-related or idiopathic
Lifestyle factors	Alcohol abuse, smoking, immobilisation
Androgen deficency	Idiopathic, hormonal suppressive therapy
Medications	Glucocorticoids, anticonvulsant medications, chemotherapeutics
Systemic illnesses	Adrenal hyperglucocorticoidism Hyperparathyroidism Hyperthyroidism Chronic obstructive pulmonary disease Gastrointestinal disorders Chronic ilnflammatory diseases (ie reumatoid arthritis)

Diagnosis

The diagnosis of osteoporosis is based on bone mineral density (BMD) measurements. The gold standard is dual-energy X-ray absorptiometry (DXA), which calculates the bone mass per unit area (g/cm^2), figure 9.

Sites of measurement are usually total hip, femoral neck and spine. The measurements are most often presented as T-score, which describes the individuals BMD in terms of the number of standard deviations by which it differs from the mean peak bone density of young, healthy adults. According to World Health Organisation, the diagnostic criterion for osteoporosis is a T-score below -2.5 [58]. Low bone density or osteopenia is defined as a T-score between -1 and -2.5 and normal BMD as a T-score above -1. BMD measurements can also be presented as Z-score, the number of standard deviations the

BMD differs from the mean value in an age and sex-matched population; this is mostly applied in children and young individuals. However, this definition applies only to women and there is even today no definition of male osteoporosis.

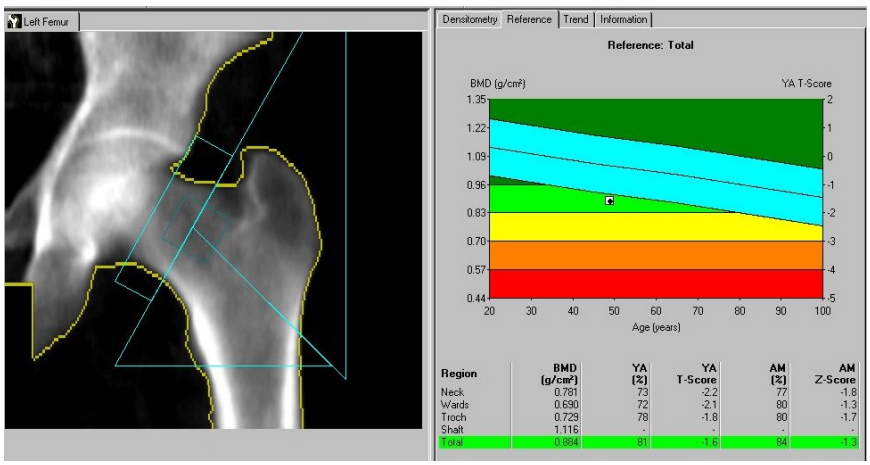


Figure 9. Results from a typical DXA scan showing the results from the hip

Although measurement of bone mineral density with DXA still is considered the gold standard for diagnosis of osteoporosis, it has some limitations. Bone strength is determined, not only by bone mass, but also by bone dimensions, microstructure and material properties. The cortical and trabecular microarchitecture is critical to bone mechanical properties, however, changes in these areas may not be detected by BMD measurement [59–61]. DXA is a fast, safe and inexpensive method. However, in the light of the growing evidence of the importance of microarchitectural changes in bone geometry with age and hormonal disturbances, it seems too blunt an instrument when assessing risk of fragility fracture. In addition, the scan can be distorted by especially soft-tissue calcification and degenerative changes in the spine in older individuals, resulting in a false high BMD [62].

Risk factors of fragility fracture

Low bone density is a major risk factor for sustaining a fracture, just as hypertension is for stroke. However, the majority of those who fracture are not osteoporotic by definition; most fragility fractures occur in patients with osteopenia (T-score between -1 and -2.5) [63], thus other factors must be involved.

Age is the single most important risk factor for sustaining a fragility fracture, which is illustrated by the fact that between the ages of 50 to 80, the risk of fracture increases 30-fold, independent of BMD [64]. Other factors that increase the risk of fragility fracture include female gender, long-term corticosteroid treatment, smoking and excessive alcohol intake. Having a previous fracture increases the risk of a future fracture 2- to 4-fold [65].

Fracture risk assessment

The multifactorial nature of fracture risk means that BMD does not capture non-skeletal determinants of risk of fracture. Because of the limitations of DXA, tools to better predict future fracture risk have been developed in various forms, so called Fracture Risk Assessment Tools. The most commonly used is FRAX® [66], figure 10; a web-based tool which calculates the 10-year absolute fracture risk for major osteoporotic fracture ,MOF (hip, wrist, humerus and clinical spine), and for hip fracture, separately, including several of the known risk factors of osteoporosis such as age, sex and prior fragility fracture among others. It can be calculated with or without BMD.

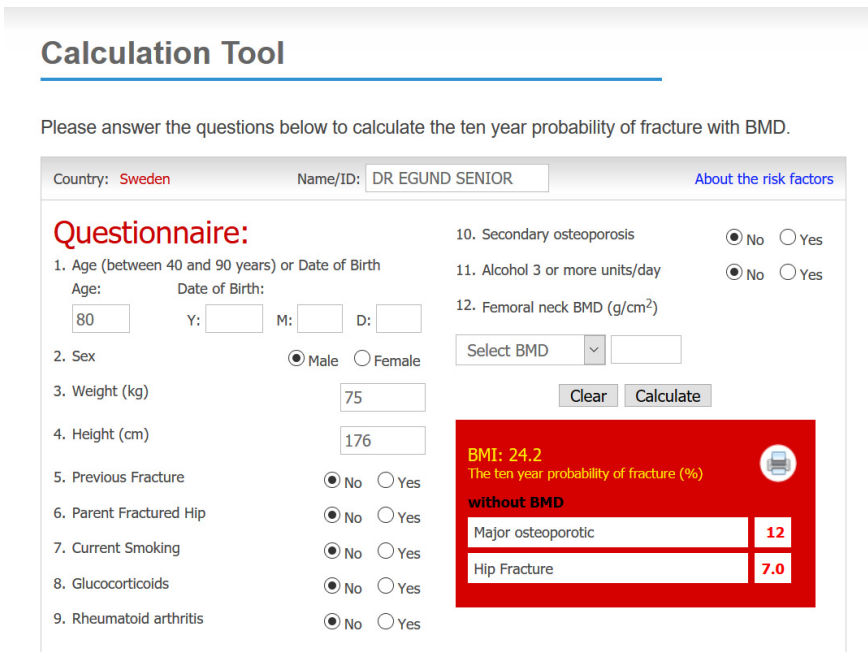


Figure 10. FRAX® calculation for the authors father

By implementation of FRAX, national guidelines have been issued [67]; FRAX is used to select the appropriate group of patients (those with a calculated high risk of fragility fracture) for DXA measurement and osteoporosis treatment. But FRAX has a limitation as it does not include former falls. There are also other prediction tools such as the Garvan fracture risk calculator [68] and Qfracture (UK only) [69], which also includes falls risk.

Treatment of osteoporosis

Treatment of osteoporosis and the prevention of future fragility fractures are multi-factorial and include non-pharmacological and pharmacological interventions.

Lifestyle changes are vital, in particular smoking cession and decreasing alcohol intake. Existing comorbidities, especially those causing secondary osteoporosis, should be treated to optimize the individual and in the elderly, an additional assessment of risk of falling is important in order to facilitate preventive measures in reducing falls. Weight bearing and aerobic exercise is recommended as regular exercise is not only beneficial to the skeleton, it also increases muscle mass, strength and improves balance, and has been shown to reduce the risk of falls by about 25% in frail elderly persons [70]. Adapted balance and coordination training can be used also at very advanced age.

Calcium supplementation may prevent bone loss or even mildly increase BMD [71]. Oral vitamin D supplementation between about 800 IU daily appears to reduce the risk of hip and any non-vertebral fractures in very elderly persons [72]. However, the use of vitamin D and calcium supplementation in the general population is not supported by evidence [73]. Nevertheless, for patients with osteoporosis, calcium and vitamin D supplementation should be used as an adjunct to other pharmacological interventions rather than as monotherapy.

The primary goal of pharmacological therapy in patients with osteoporosis is to reduce the risk of future fracture, not just to increase bone density. Various types of treatment are available; however, most studies on efficacy and safety only include women. Medications can be divided into anti-resorptive agents, which reduce bone resorption more than promote bone formation and thereby suppress bone turnover and loss, and anabolic agents, which stimulate bone formation more than reduce bone resorption. The first line treatment is oral bisphosphonates, anti-resorptive agents which reduces the risk of hip and vertebral fracture up to 50-60% in women [74]. Again, evidence is weaker in men due to few studies [75,76]. Other anti-resorptive agents, intravenously given bisphosphonates [77,78] and subcutaneously administered denozumab [79] leads to higher adherence to therapy and subsequently higher efficacy.

The distal radius fracture

Almost one sixth of all fractures overall are a distal radius fracture [80]. It is often regarded as a simple fracture, which heals with no complications. But it is evident that this is not true for all, as one out of five still have high disability and pain even after one year [81,82].

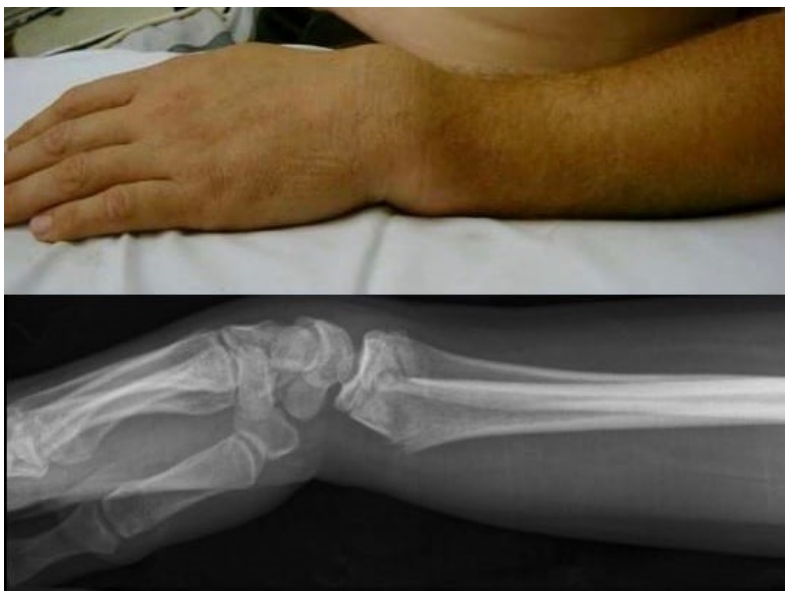


Figure 11. Distal radius fracture. https://litfl.com/colles-fracture

A fracture to the distal radius is not only the most common fracture of them all, it is also the signal fracture for osteoporosis and future fragility fractures [83,84]. Forearm fractures reflect deficits in bone mineral throughout the skeleton, not just at the forearm. Therefore, it is essential to recognize the clinical importance of not only treating the fracture itself but also in identifying individuals at risk of future major and disabling fractures.

Epidemiology

Distal radius fractures affect all ages although the incidence has a bimodal distribution. The incidence is high in children (due to a weak metaphysis during rapid growth), drops during young adulthood and increases again in older adults [85], figure 12. There is also a sex difference in the incidence rates. Boys, and men up to the age of 49 are at higher risk of distal radius fracture than girls and younger women [86]. Beyond that age,

distal radius fracture increases markedly in women. In men the incidence remains relatively low (15/10.000 person years) until the age of 80 (31/10.000 person years) [87,88].

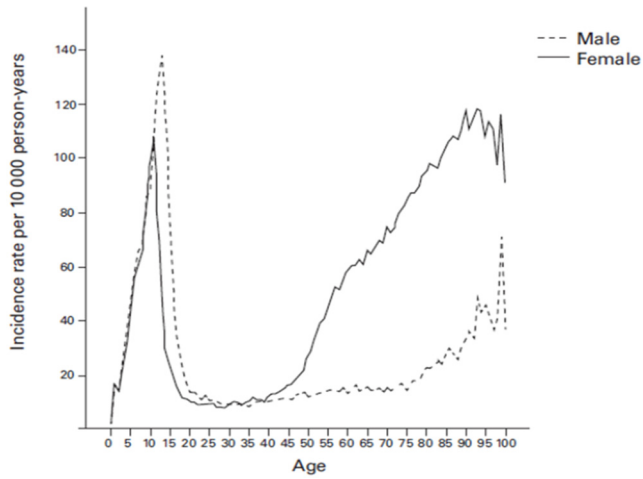


Figure 12. Line graph showing the incidence rate for all fractures of the distal radius in Sweden during 2005 to 2010 related to age and gender. Mellstrand-Navarro et al. From Bone Joint and Journal 2014 [89]

In Scandinavia, incidence rates for both men and women are higher than in the rest of Europe [90]. In a recently published study the incidence of distal radius fracture in adults in Southern Sweden were 40/10.000 person years with a 1:3 male to female ratio [88]. The reasons are not fully understood but possible explanations include vitamin-D deficiency, outdoor risks from adverse weather conditions a higher prevalence of osteoporosis [52]. Indeed, in a Norwegian cross-sectional study of older men from the age of 50 with distal radius fracture as many as 33% had a T-score ≤-2.5. This is a rather high number and whether it applies to the rest of Scandinavian men is unknown.

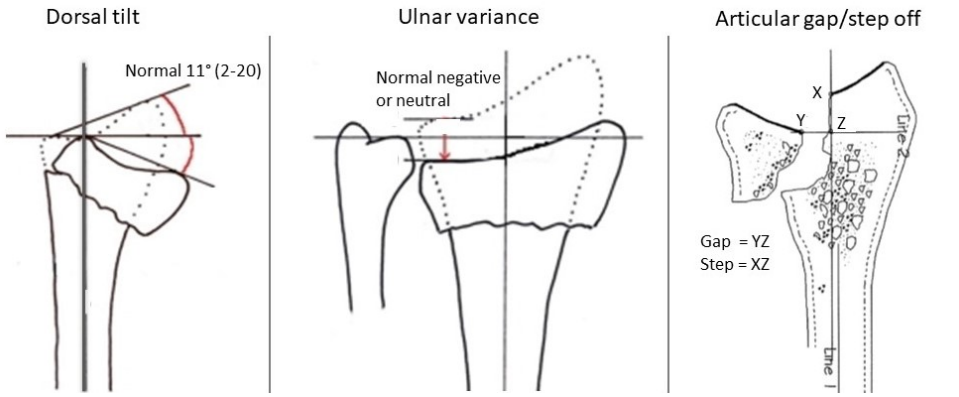
The most common causes of distal radius fracture in children and young adults are playing/sport activities and motor vehicle accidents. In contrast, a distal radius fracture in older adults is most often caused by a fall from a standing height with outstretched hand [91]. Compared to women, men aged 50 years or older are more likely to sustain their fracture from a higher degree of trauma [87].

Radiographic evaluation and fracture classification

Distal radius fractures are a heterogeneous entity with various fracture patterns which reflects different trauma mechanisms. The most common is the dorsally displaced

fracture (Colle´s), but they can also be displaced volar (Smith's) or partially intra-articular (Barton´s, Chauffeur's). The degree of articular involvement and comminution is highly variable and depends on degree of trauma and also bone properties as osteoporotic bone is prone to more comminution [92].

When assessing a distal radius fracture, radiographic evaluation is essential. It includes a posteroanterior and a lateral view and in these views, dorsal tilt, ulnar variance, intra-articular step off or gap and radial inclination can be measured. The radiographic parameters used in this thesis are shown in figure 13.



The angle between a line connecting the dorsal and volar lips of the distal radius and a line perpendicular to the central axis of the radius [93]

The distance between a horizontal line drawn from the mid-articular surface of the sigmoid notch of radius (central reference point) and a line parallel to the carpal surface of the ulnar head [94]

Step off is the vertical height between the two fracture fragments and articular gap the horizontal distance between the two articular fracture fragments.

Figure 13. Illustration and definition of the radiographic measurements of the distal radius used in this thesis. The stapled lines demonstrate normal anatomy.

There are several classification systems of distal radius fracture; however, none has shown to be useful in predicting prognosis and guiding in choice of treatment [95]. Furthermore, the inter- and intra-observer reliability are poor [96]. Still, classifications are widely used and in research they are used to describe the fractures of the included study participants. The AO-classification system, which is the most detailed with a total of 27 subgroups, has shown to be the most reliable in term of inter and intra-observer reliability when restricted to its three main types: A extra-articular, B partially intra-articular and C intra-articular [96], see figure 14.

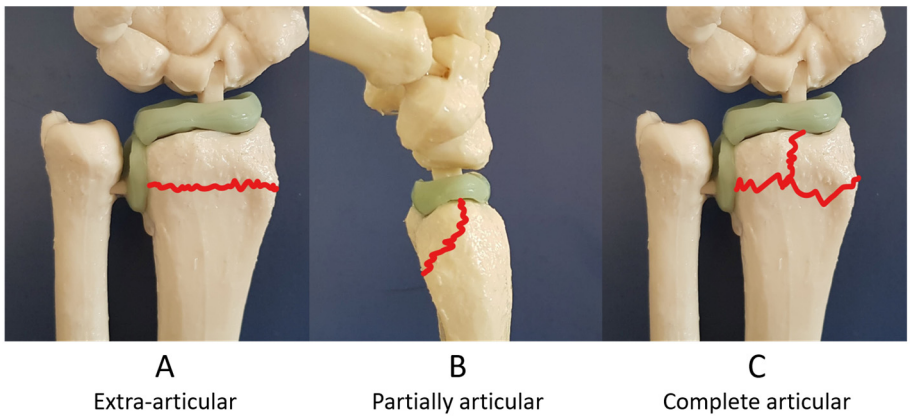


Figure 14. AO classification in its main 3 types

Treatment

In the younger population, there is now consensus on acceptable fracture appearance and when surgery is warranted. Common radiographic criteria for a displaced fracture are usually ulnar variance of more than 2 mm and/or intraarticular step-off or gap more than 1 mm and/or dorsal angulation of more than 10° or a volar angulation of more than 25° [97]. However, older patients from the age of 65 seem to tolerate displacement better [98,99], perhaps based on the assumption of lower functional demands; but even in active elderly displacement does not necessarily mean greater disability [100].

Most distal radius fractures are treated non-operatively [89]. Undisplaced fractures are treated in a short arm cast for 4-5 weeks. Displaced fractures are treated with closed reduction under local anaesthesia at the emergency ward before immobilisation. If the reduction results in acceptable radiographical appearance, the patient is re examined after 7-10 days and in case of radiographical re dislocation, the patient is offered an operation. If the fracture is highly unstable (including Smith´s and most Barton fractures) or the reduction at the emergency ward is unacceptable, the patient is primarily recommended surgery. The chronological and physiological age of the patient, preferences and demands are always considered in the decision to operate.

Surgical treatment

There are several methods and techniques to surgically treat a distal radius fracture, figure 15. At the time of investigation, 1999 to 2007, the preferred method of treating unstable and displaced radius fractures was closed reduction and external fixation.

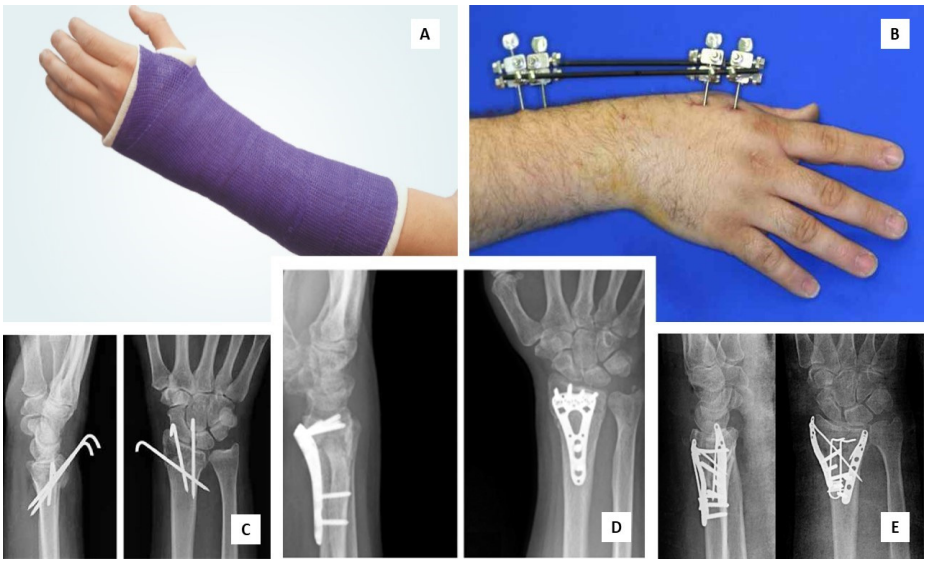


Figure 15. Types of treatment of distal radius fracture. A cast. B external fixator. C percutanous pinning. D volar plate. E fragment specific internal fixation.

Another common method is percutaneous pinning. During the last decade internal fixation with volar plates with locking screws has become widely used; a method providing stable anatomical fixation and allowing for early postoperative mobilisation [(89)]. However, despite a copious number of studies on surgical treatment of distal radius fracture, there is still not enough evidence on which method is superior [(101–103)]. The volar plates are showing some advantages especially when compared to external fixation in regards of earlier mobilisation and better patient-reported outcome early after treatment, although diminished at one year after surgery [(81,104)]

Outcome assessment

As physicians, we can measure the effect of the treatment given on a palette of parameters. Outcome assessment has traditionally relied on the examiner's evaluation, based on objective measures such as radiographic appearance, range of motion and grip strength and the absence of complications. However, objective measures of outcome do not necessarily reflect the patient's perception and during the recent decade there has been a shift towards a more patient-centred view with increasing interest in evaluating patient related outcome.

Radiographic assessment

Radiographic evaluation is almost obligatory in the outcome assessment. Still, correlations between objective and subjective outcomes and the degree of radiographic deformity is controversial [105–107]. Nevertheless, radiographic assessment is helpful in predicting fracture instability [108].

Functional outcome

Grip strength and range of motion is the commonly used objective functional outcomes. Grip strength is most often measured with the Jamar hand dynamometer. Range of motion (ROM) in the radio-carpal joint is measured in degrees with a goniometer and includes extension-flexion and radial-ulnar deviation; pronation-supination in both the proximal and the distal radio-ulnar joints. The grip strength and range of motion is then compared to the contralateral side. Although clinical objective functional outcomes are always evaluated when assessing patients with distal radius fractures, they have only shown to have weak to moderate association to patient-reported disability and pain [109,110].

Patient Reported Outcome Measurements

Patient reported outcome measurements, so-called PROM´s, are tools developed to measure the patient's own perception of function, pain and quality of life. They were first developed in the 1970´s and are now extensively used not only in the research setting but also in the clinic. They can be divided into generic, region- and finally joint-specific.

The SF-36 is the most established generic health status measure [111]. It produces eight scales in various aspects of physical and mental health and is compressible into two overall scores: the physical component score (PCS) and the mental component score (MCS). Each is normalized to a mean of 50 and standard deviation of 10 compared to the general population, with higher score indicating better quality of life.

When evaluating patient related outcome after distal radius fracture, the DASH questionnaire is the most widely used [112]. It aims to capture the perception of upper arm function and although being a region-specific instrument it has proven to have high responsiveness to change after distal radius fracture [113]. It consists of 30 items that on a 5-likert scale evaluates different aspects of function of the upper limb, providing an overall score of 0-100; higher scores indicating higher disability.

Sick leave

The hand is of crucial importance for all activities of daily living and work. To most individuals, work is a vital part of life and being able to work is associated with better health, increased self-esteem and financial independency [114].

In the working age population, a fracture often results in incapacity to work and sick leave is an issue that clinicians must deal with every day. While there is an enormous amount of current literature regarding the management and evaluation of orthopaedic injuries; outcomes including sick leave are not much studied [115]. This is contradictory, as early identification of factors associated with a greater risk of long time of work may reduce both the personal and the socio-economic burden of orthopaedic trauma. Working capacity can also be seen as a marker of post-fracture functioning as well as a measure of treatment success.

Some of the factors of importance to sick leave after trauma in general are higher age, lower education and severity of the illness/injury [115]. With regards to sick leave after distal radius fracture, one study has specifically addressed this question to date [116], finding, that patients with high self-reported disability and high occupational demand at baseline are at risk of prolonged work loss; men and women were not considered separately thus information on men is missing.

Rationale for this thesis

In summary, the distal radius fracture is the most common fracture of them all and it serves as a red flag for osteoporosis. As such, thousands of studies of various aspects of distal radius fracture have been conducted; as of April 2020, the search term "distal radius fracture" on the search engine Pubmed generates more than 7000 publications.

However, only a handful of studies had investigated bone mass in men with distal radius fracture, finding a surprisingly high prevalence of osteoporosis. No study has included younger men. So, the original main aim of this study was to explore the bone mass in men *of all ages* with distal radius fracture and risk factors of osteoporosis.

After the publication of the first paper, we asked ourselves if there was an underlying cause of the observed lower BMD in men with distal radius fracture? In women, the incidence of distal radius fracture increases markedly when entering menopause. Men don't experience a natural dip in sex hormones like women do, but sex hormones might still be an explanation. To date, only elderly men with fracture have been investigated regarding sex hormones. So, the next study was designed to address this gap in knowledge, studying younger men with distal radius fracture and their sex hormone profile.

The distal radius fractures have long been regarded simple fractures that heal nicely, but studies and reality has proven otherwise. It can cause prolonged pain, incapacity to work and due to the large number of fractures, also great socio-economic cost. We know now, that in younger individuals an inadequate reduction most often will result in a poor outcome. In elderly, research is conflicting as many studies show that radiographic and functional outcome is not correlated while other say that they are. In the light of the growing elderly population and hence growing number of fractures, we aimed at gaining new knowledge; we looked at this fracture from a different angel and explored differences in fracture and bone properties and their relation to self-reported outcome in the young and the elderly.

Finally, to address another gap in knowledge, we wanted to explore determinants for length of sick leave after distal radius fracture. Although those of working age are not at highest risk of distal radius fracture, the sheer number of fractures in this population makes it a very important aspect to address.

Aims

The overall aim of this thesis was to comprehensively study adult men with distal radius fracture and specifically address the bone mass of men of all ages and in addition, explore determinants for self-reported outcome and sick leave.

Specific research questions

Paper I	How does BMD differ between men with distal radius fracture and a control group representative of the background population?
Paper II	Sex hormones are crucial to skeletal health in adolescence and older age. We showed in paper I, that even younger men with distal radius fracture have lower BMD and, in this paper, we hypothesize, that lower levels of testosterone and estradiol in this group with fracture could be an explanatory factor.
Paper III	Self-reported outcome after distal radius fracture are different between young and elderly. But how does self-reported outcome relate to fracture appearance, BMD and fracture risk in young and elderly men?
Paper IV	Sick leave following a fracture is a common negative consequence. But what factors are of importance after distal radius fracture and what is the impact of patient- and fracture related factors, respectively, on length of sick leave?

Patients and Methods

Study design and participants

This study was conducted at the Department of Orthopedics, Skåne University Hospital, Malmö, Skåne, during 2003-2007. Men, resident in the catchment area of the hospital, aged 20 years and above presenting with a DRF resulting from any trauma were eligible for the study. Patients who did not speak or understand Swedish and those with multiple fractures were excluded since the protocol included self-reported outcome instruments. No other exclusion criteria, such as co-morbidities or medications, were applied.

It was designed in two arms, a retrospective and a prospective, in order to address the specific aims of the overall study i.e. investigation of bone mass at inclusion and longitudinal follow-up of functional outcome post-fracture. This design was also necessary due to the relatively low incidence of distal radius fracture in men, thus allowing for a larger cohort to be collected in a shorter time. A flowchart describing the study is presented below.

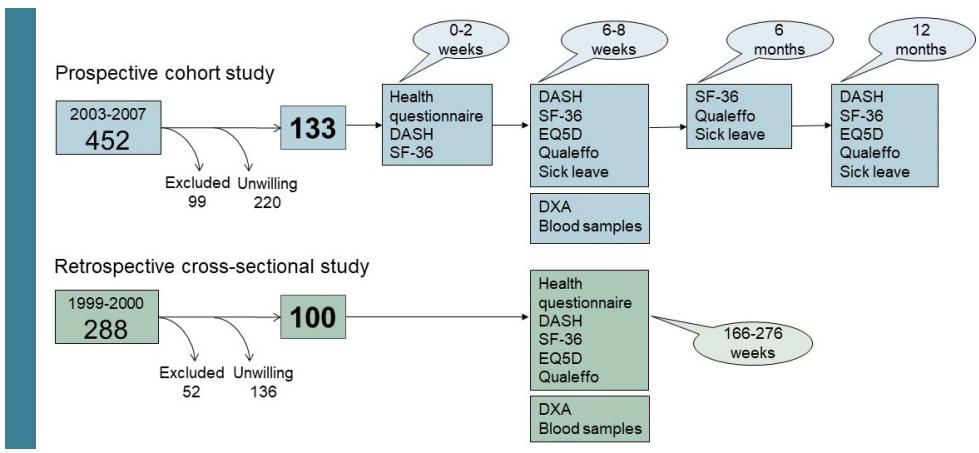


Figure 16. Flowchart of the study illustrating the pro- and retrospective arms and time of investigations according to fracture occurrence.

In the retrospective cross-sectional arm, all men who had consulted the orthopaedic or radiology department after sustaining a distal radius fracture during 1999 to 2000 were identified by reviewing patient case files and radiology reports. During fall 2003 these men were invited by mail to participate in the study and were examined during a single visit to the Osteoporosis Research Unit between December 2003 and June 2004. Time from fracture to examination was mean 4.1 years, range 3.2-5.3.

The prospective cohort study was conducted between March 2003 and March 2007 and all men presenting with acute distal radius fracture were asked to participate in the study. The fracture patients were identified through the admission records of the Emergency Department or at the one-week routine control at the out-patient clinic.

At inclusion all participants completed a comprehensive questionnaire on health status, medication, previous fractures, family history, educational level and life-style factors such as diet, tobacco, alcohol consumption and physical activity.

Participants in the prospective arm were examined 6-8 weeks later (mean 8 weeks, range 4-19 weeks) and were followed up at 3, 6 and again at 12 months after fracture by questionnaires sent by mail.

A total of 738 men who suffered a distal radius fracture were identified (288 in the retrospective arm, 452 in the prospective arm). 151 patients were excluded: 42 had a non-acute fracture in the prospective part of the study; 26 had multiple fractures; 46 were deceased prior to investigation; 18 patients were not resident in Malmö and 19 did not speak Swedish). Of the remaining 589 eligible patients, 233 agreed to participate in the study (n= 100 in the retrospective arm, n= 133 in the prospective arm), giving a response rate of 40%.

Treatment

All participants were treated according to standard, established treatment protocol used since 1998 at Skåne University Hospital, which have shown good final subjective outcome, figure 17 [97]. Briefly, undisplaced or minimally displaced fractures are treated in a short arm cast for 4-5 weeks, displaced fractures with closed reduction and cast, and highly unstable fractures with surgery. Displacement according to treatment protocol is defined as dorsal tilt >10° (>20° from normal anatomy) and/or ulnar variance >2mm. For the statistical analysis, undisplaced distal radius fracture compromise fractures in anatomical normal position, minimally displaced and acceptable displaced fractures.

All displaced fractures are followed with radiographs at 7-10 days. If the fracture was totally undisplaced (20 patients), no further radiographic evaluation was performed. Chronological and biological age, preferences and demands are taken into

consideration. At time of investigation closed reduction and external fixation were the preferred treatment of unstable and displaced radius fractures.

Patients attend a physiotherapist within a week after cast or external fixator removal, with final check-up 3-4 weeks later. Unfortunately, this evaluation documentation was incomplete and could not therefore be included as part of the analyses for the study.

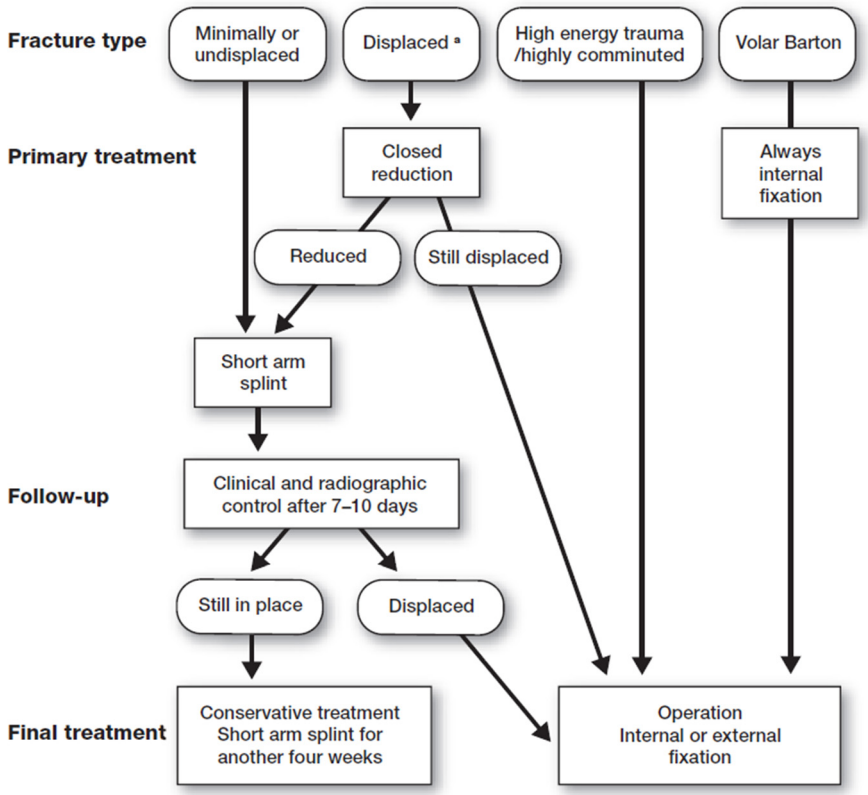


Figure 17. Treatment protocol for distal radius fractures used since 1998 at Skåne University Hospital

Control group

To enable comparison of men with distal radius fracture to the background population, an age-matched control group was used. The control group consisted of 643 men aged 24-81 years who had been examined at the orthopaedic research clinic during 2003-

2013 as part of two different studies in a collaboration with the Reproductive Research Unit, Skåne University Hospital, Malmö.

The first study was part of the European Male Aging Study (EMAS). 409 men aged 41-81 years and residents in Malmö, Skåne, had been examined between June 2003 and March 2005. EMAS is a multicentre prospective cohort study designed to examine the prevalence, incidence and geographical distribution of gender-specific and general symptoms of ageing in men. In eight European centres, men had been randomly selected from the population registries and were invited by mail. No exclusion criteria were applied. The response rate in this study was 45% [117].

In the second study, men aged 24-58 and residents in Malmö, Skåne, were enrolled as controls in studies of infertility and childhood cancer survivors between March 2010 and January 2013 [118,119]. All controls had been randomly selected from the population registry and were invited by mail. The only exclusion criteria were prior or present malignant disease. Of the 977 approached, 234 (24%) agreed to participate.

Examination and measurements

All participants and controls underwent a baseline examination including BMD measurement by dual-energy X-ray absorptiometry (DXA), anthropometrics, blood sampling and completed health-related questionnaires.

DXA measurement

Bone mineral density (g/cm²) at the femoral neck (FN), total hip (TH) and lumbar spine, L2-L4 (LS) was measured in 207 fracture patients and 545 controls. BMD was assessed using DXA. Lunar Prodigy were used for all fracture patients and the majority of controls (570 of 643); for the final 73 controls instrument failure obliged us to use the Lunar iDEXA instead. These participants composed a significant part of the younger controls and they were included after performing a cross-calibration to compensate for the small variation. The BMD data used in the statistical analyses have been adjusted to the Prodigy.

We applied the operational WHO definition for osteoporosis (T-score ≤ -2.5 SD), osteopenia (T-score > -2.5 SD and < -1.0 SD) and normal bone density (T-score ≥ -1) and T-score calculations were derived from the DXA manufacturer supplied reference population, i.e. males aged 20-39 of USA/European origin [120]. In 2013 the International Osteoporosis Foundation stated that female reference data should also be used to calculate T-scores for men since fracture occurs at the same absolute BMD in

men and women [121]. We presented T-scores derived from both the male and the female reference data since T-scores based on male reference data are widely implemented clinically, male-specific reference databases are used by the major densitometer manufacturers to calculate T-scores for men, and it allows for comparison with published studies [122].

T-scores based on female reference data was calculated using the following formula:

$$\text{T-score}_{\text{female ref}} = (\text{BMD}_{\text{participant}} - \text{BMD}_{\text{female ref}}) / \text{SD}_{\text{female ref}}$$

Z-scores, adjusted for age and weight, were also obtained from the machine.

FRAX

10-year absolute fracture probability was calculated by FRAX for major osteoporotic fracture (MOF: hip, wrist, humerus and clinical spine) and for hip fracture by using the Swedish version of the web-based tool. The algorithm includes the following risk factors: age, prior fracture, parental history of hip fracture, low body weight or BMI, use of glucocorticoids of 5 mg or more for 3 months or more, rheumatoid arthritis, current cigarette smoking, excessive alcohol intake of 3 units or more daily and other causes of secondary osteoporosis. It was calculated with femoral neck BMD.

Data collection

Degree of trauma was recorded by questionnaire and the fracture cases were divided into either low or high trauma category. Low energy trauma was defined as a fall from standing height or less. High trauma was defined as fall from any height or traffic accident.

Comorbidities was recorded from the initial questionnaire and Charlson Comorbidity Index (CCI) was calculated as a measure of pre-existing comorbidity [123].

The occurrence of complications to the fracture treatment was recorded by retrospectively reviewing the medical files of the participants, both electronic and paper files (Region Archive, Lund).

Radiographic assessment and fracture classification

The fractures of participants in the prospective arm were radiographically evaluated during 2015 by two highly experienced radiologists (Niels Egund and Jack Besjakov).

The examination, including standard posteroanterior and a lateral view, at the initial presentation and at the follow-up evaluation 1-2 weeks later were assessed.

Fractures were classified according to the AO-systems 3 main types: Type A, extra-articular; B partial articular and C complete intra-articular [124]. We also recorded if the fracture belonged to the more severe subgroup 3 (comminution).

Dorsal tilt (degrees), ulnar variance (mm), intra-articular gap and step-off (mm) were the radiographic parameters measured as previously described.

Patient Reported Outcome Measurements (PROM´s)

The Disability of the Arm, Shoulder and Hand questionnaire (DASH, Swedish version) were used to evaluate disability after distal radius fracture. In addition, in order to further understand the importance of pain on sick leave, we specifically analysed the pain question within the instrument.

As measurements of global health, the SF-36 questionnaire and the EQ-5D-3L was used. The EQ-5D-3L consists of the EQ-5D descriptive system and the EQ visual analogue scale, EQ VAS. The latter records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable Health state' and 'Worst imaginable Health state'.

Sick leave

The participants in the prospective arm were followed up at continuous time points and they first reported on sick leave at the time of the exam 6-8 weeks after fracture. During the following year they were sent questionnaires by mail at 3, 6 and 12 months after fracture including a form regarding sick leave.

The participants description of their job situation in the initial questionnaire was used for classification of work demand according to Office of Administration Law Judges (OALJ) Law Library (US Department of Labour) [125], into sedentary, light, medium, heavy and very heavy by a research nurse and the author, separately. When disagreements in classification occurred, consensus was reached after discussion.

Hormone assays

Serum values of total testosterone (TT), total estradiol (E2), luteinizing hormone (LH), follicle stimulating hormone, (FSH) and sex hormone binding globulin (SHBG) were measured. Detailed descriptions of the methods of analysis are presented in Appendix I. All analyses were performed at the Department of Clinical Chemistry, Skåne University Hospital, Sweden.

E2 in fracture cases was analysed with liquid chromatography-tandem mass spectrometry method (LC-MS/MS). Controls were assayed using a modified DELFIA, which has lower sensitivity. To harmonise data in cases and controls, DELFIA values were transformed to LC-MS/MS equivalent values as follows: frozen sera from 30 controls was re-analysed with LC-MS/MS and the linear curve of best fit determined. Using the formula described in the appendix, all control values were transformed (see Appendix II).

Free testosterone (cFT) was calculated as recommended by Vermeulen et al [126].

Measured bioavailable E2 was not available, instead we calculated the ratio E2/SHBG which has been shown to be a reasonable surrogate [36].

For fracture cases venous blood was drawn non-fasted between 08.00-20.00; for controls, fasted blood was drawn between 08.00-10.00. Serum from fracture cases was analysed in batch during late 2015 and the controls, continuously during enrolment (2010-2013). In younger men, testosterone and estradiol have diurnal variations, with the highest concentrations before 10 a.m. To account for the all-day blood sampling of fracture patients, we adjusted the values from the fracture cases by time of sampling i.e. 08.00-10.00, 10.00-14.00 and 14.00-20.00. Conversion factors were calculated (see example below), using the mean hormone values in each group; with the early group as reference category

$$TT^{10.00\text{-}14.00} = [TT^{8.00\text{-}10.00} - TT^{10.00\text{-}14.00} / TT^{08.00\text{-}10.00}] + 1$$

Age, BMI or proportion of smokers did not differ significantly between the three time of sampling groups.

Samples from fracture cases were stored for 8-12 years at –80°C. To adjust for potential evaporation [127], we first measured sodium (Na^+) concentration, which was found to be higher than the normal mean 140nmol/L (mean and median 143 (IQR:141-144)). We then applied the correction factor 0.98(140/143) to all hormone measurements and SHBG. There were no freeze-thaw cycles.

During the inclusion period of controls, the analysis methods for testosterone, LH, SHBG and FSH changed. To ensure comparability, duplicate measurements were performed, and values transformed to equivalent values from the currently used assay methods described (see Appendix II).

Statistical analysis

Continuous data are presented as mean with standard deviation (SD) and/or median and interquartile range and 95% confidence intervals were calculated when appropriate.

Categorical data are expressed as number and percentage.

Quantitative data was tested for normality using Kolmogorov-Smirnov test. Normally distributed data were analysed using independent unpaired t-test or ANOVA for continuous variables and Chi-square test for comparisons between categorical variables and non-normally distributed data using Mann-Whitney or Kruskal-Wallis.

In all papers, a p-value less than 0.05 was considered indicative of nominal statistical significance. IBM SPSS Statistics version 22-25 was used for all statistical analyses.

Paper I

In this study, data from participants from both the retrospective and prospective arm was merged and analysed as a single dataset after finding no differences in age at fracture, BMI or BMD between the two arms.

Age related decrease in BMD in men is considered to become evident around 60-70 years of age, with low BMD rare in otherwise healthy men below age 40 [128], therefore in the analyses the cases and controls were divided into 3 age groups: 20-39 years, 40-64 and 65 and above. Regression analysis of absolute BMD values was performed, and data adjusted for age and BMI. Odds ratios (OR) and 95% confidence intervals (95% CI) for osteoporosis were estimated in logistic regression analyses adjusted for BMI and age.

Paper II

Univariate regression analysis was performed to compare BMD and sex hormone levels in men with fracture and controls. Data was adjusted for confounders (age, BMI and smoking). Binary logistic regression analysis was applied to calculate odds ratio (OR) for fracture, comparing those with low and normal levels of testosterone, free testosterone and estradiol, adjusting for age, BMI and smoking.

Paper III

Participants were divided into: 'young' below age 65 and 'elderly' 65 and above (since most distal radius fracture studies use this threshold); additionally, osteoporosis in men is more frequent from age 60-70.

We dichotomized DASH scores into good (<15) or poor (≥15) outcome, based on the age specific population norm (US adult population mean DASH 10) and to enable comparison with a previous study [129].

We applied multiple linear regression to determine whether BMD was predictive of functional outcome using continuous DASH scores at 12 months. Logistic regression analysis assessed BMD as a predictor of outcome independent of age, fracture classification, treatment, complications, radiographic parameters and CCI.

Paper IV

Sick leave was analysed in three clinically relevant groups: 'short' 0-6 weeks (immobilization and two weeks rehabilitation), 'intermediate' 7-12 weeks (allowing for longer rehabilitation) and 'prolonged sick leave' ≥13 weeks.

Work demand was dichotomized into "sedentary to medium" and "heavy to very heavy" due to low numbers in each of the 5 groups.

Association between sick leave group and different patient and fracture related factors were analysed and depending on the variable tested, parametric (t-test, ANCOVA or chi-square) or non-parametric (Mann-Whitney or Kruskal-Wallis) tests were applied.

Spearman´s rho (r^s) was used for bivariate correlation analysis between length of sick leave and patient and fracture related factors; the method allows for inclusion of outliers, non-normally distributed or non-linearly related variables.

We performed stepwise multiple linear regression to identify potential predictors of length of sick leave. The ground model (model 1) included age, CCI and work demand (i.e. non-fracture related factors) while model 2 added treatment (cast, closed reduction and cast or surgery). For the explanatory models we added disability, pain, and global health.

Ethical considerations

All parts of the study were approved by the regional ethical review board in Lund, Sweden (LU 788 02 November 11th, 200, Lund University). It was performed in compliance with the Helsinki Declaration. All participants and controls were informed

of the purpose of the study and gave their signed informed consent before being enrolled.

All eligible participants were treated with respect and inclusion was not limited on grounds of ethnicity or religious beliefs. They were given the same fracture treatment whether agreeing or declining to participate in the study.

The risk of harm was considered to be low due to the observational character of this study. A phlebotomy induces only little risk and discomfort and the exposure to radiation is minimal from the DXA scan.

Results

Paper I - High Prevalence of Osteoporosis in Men with Distal Radius Fracture: A Cross-sectional Controlled Study of 233 Men

Background

Most women with distal radius fracture have sub-normal BMD. Whether this is also the case for men is less clear as surprisingly few studies have specifically investigated BMD in men with distal radius and all have had emphasis on the elderly. However, distal radius fractures also occur in younger men and we can hypothesise that reduced bone mass may already be present at an early age. Thus, the purpose of this cross-sectional, controlled study was to evaluate BMD in adult men of *all* ages with distal radius fracture.

Patients and Methods

In this case control study, data from participants from both the retrospective and prospective arm was used. A total of 233 men with distal radius fracture was compared to 643 controls. Fractures regardless of degree of trauma were included. BMD was measured at femoral neck, total hip and lumbar spine; osteoporosis was defined as a T-score ≤ -2.5 SD at any of the measured sites. Patients and controls were divided into 3 age-groups: 20-39 years, 40-64 and 65 and above.

Results

The mean age for distal radius fracture was 52.2 years (20.6-88.3). There was no significant difference in BMD, T-scores or Z-scores at any site between those with high or low energy trauma.

The controls were slightly younger than the fracture group and there was a tendency towards more comorbidities in the fracture group (table 3).

Table 3. Demographic variables and clinical characteristics in the fracture group, divided into prospective and retrospective cohort and as a whole, and controls*

	Prospective fracture group *n* = 133		Retrospective fracture group *n* = 100		Fracture group *n* = 233		Controls *n* = 643	
Age at fracture(y)	54±18 (21-88)		50±15 (23-84)		52±17 (21-88)		NA	
Age at DXA (y)	54±18 (21-88)		55±15 (27-88)		54±17 (21-88)		51±15 (24-81)	
Height (cm)	178±7 (159-194)		178±6.3 (164-198)		178±6 (159-198)		179±7 (159-199	
Weight (kg)	82±14 (46-144)		86±13 (66-125)		84±13 (46-144)		84±13 (52-136)	
BMI (kg/m²)	26.0±3.8 (16-40.8)		27.2±4.0 (20.0-41.6)		26.5±3.9 (16-41.6)		26.2±3.7 (18.0-45.7)	
Smoking - current	22	(16.5 %)	15	(15 %)	37	(16.4 %)	106	(16.9 %)
Smoking - former	49	(36.8 %)	43	(43 %)	92	(40.9 %)	260	(41.4 %)
Cardiovascular disease	39	(29.3 %)	23	(23 %)	62	(28.3 %)	122	(19.2 %)
Diabetes (Insulin-dependent (ID)	4	(3.0 %)	1	(1 %)	5	(2.2 %)	9	(1.4 %)
Diabetes (Non-ID)	3	(2.3 %)	4	(4 %)	7	(3.1 %)	15	(2.4 %)
Hypothyreosis	4	(3.0 %)	3	(3.0 %)	7	(3.2 %)	8	(1.3 %)
Reumatoid Arthritis	3	(2.3 %)	1	(1 %)	4	(1.7 %)	NA	
Glucocorticoid use (ever)	6	(4.5 %)	0	(0 %)	6	(2.7 %)	1	(0.2 %)
Bisphosphonate use (ever)	1	(0.8 %)	0	(0 %)	1	(0.4 %)	2	(0.3 %)
Calcium supplement	2	(1.5 %)	3	(3 %)	9	(3.9 %)	0	(0 %)
Vitamin D	2	(1.5 %)	2	(2 %)	4	(1.8 %)	0	(0 %)

*Age, height, weight and BMI are reported as mean, SD and range. NA = not available. *The total numbers may vary slightly because of missing data

Overall, men with distal radius fracture had significantly lower BMD (6.7% to 7.3%) at all sites compared to controls and adjustment for age and BMI did not alter this result. The difference in BMD between patients and controls increased with age with the largest difference observed in those aged 65 and over (10.7 to 13.8%).

In the entire group of distal radius fracture patients, and in each of the age-groups, the proportion of men with a diagnosis of osteoporosis (T-score ≤ -2.5) at any skeletal site was 3 to 5 times higher than in the controls, figure 18; the largest proportional difference was in the youngest men aged 20-39 at 8.5% compared to 1.5%, p=0.023. This increased risk of osteoporosis among men with fracture was evident even after adjustment for BMI and age (OR= 3.5, 95% CI (2.034-6.185); p<0.001).

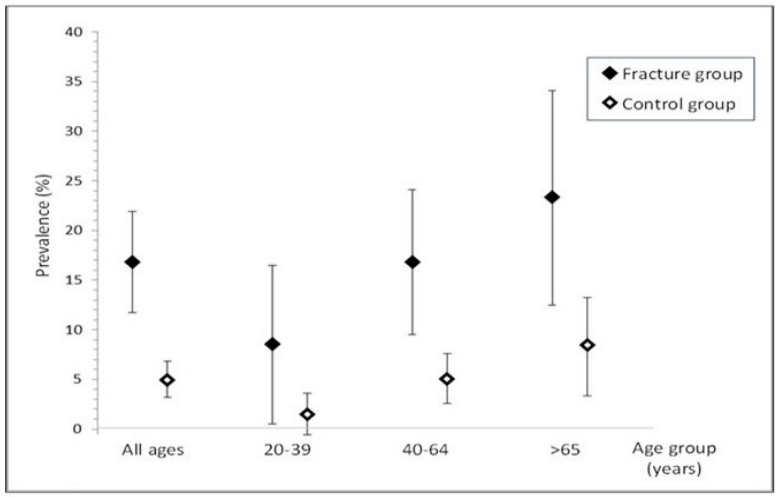


Figure 18. Prevalence of osteoporosis i.e. T≤ -2.5 at any one of the sites measured in the fracture and control group: all and divided into age groups

Conclusion

The results from this study suggest that men aged 40 and over who suffer a distal radius fracture have lower BMD and are at increased risk of skeletal fragility. Even in the younger men a trend toward a higher risk of osteoporosis was apparent. Presentation of a distal radius fracture regardless of trauma level and sex indicates that screening for osteoporosis and risk of future fractures should be considered.

Paper II - Low estradiol and testosterone and high luteinizing hormone in younger men with distal radius fracture

Background

Sex hormones have an important role in regulating skeletal growth and maintenance. Studies have shown, that in older men from the age of 70, low estradiol rather than testosterone is associated with low BMD; however, the *risk of fragility fracture* seems to be higher when both estradiol and testosterone are low. Whether this also applies to young and middle-aged men is conjecture, as sex hormone profiles in younger men with fracture has not been investigated.

This study investigates the sex hormone profile in younger men with distal radius fracture in order to elucidate if this contributes to explaining the low bone density and osteoporosis previously observed.

Patients and Methods

For this case-control study, those aged 20-50 from the retrospective and prospective arm and with available blood samples were included. This age-span was chosen to match the younger controls from the infertility/childhood cancer survivor studies with available sex hormones measurements. This left 73 men with distal radius fracture (mean age 38±9; range 20-51) to be compared to 194 age-matched controls.

Performed assays were total testosterone (TT), calculated free testosterone (cFT), luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), and total estradiol (E2). The E2/SHBG ratio was calculated as a surrogate for bioavailable E2 and the E2/TT ratio as an indicator of aromatase activity. Low TT level was defined as <10.5 nmol/L and low cFT level as <220 pmol/L. Low estradiol was defined as <73 pmol/L since below this threshold significantly higher rates of bone loss have been reported in men, similarly aged as our cohort. Data was adjusted for age, BMI and smoking.

Results

Hormone profiles are reported in table 4. Men with distal radius fracture had lower cFT (298 vs 332; p=0.008) but not TT compared to controls and there was no difference in SHBG. The proportion with low TT was almost twice as high in the fracture group (cases 21% vs controls 11%, p=0.052) and similarly, the proportion with low cFT (18% vs 8%, p=0.017).

Table 4. Sex hormone profiles in men with distal radius fracture and controls

	Adjusted $_{\text{BMI and age}}$ (mean (95% CI))				
	Fracture group *n*=73		**Controls** *n*=194		*p*-value
TT (nmol/l)*	16.0	(14.6-17.3)	16.9	(16.0-17.7)	0.264
cFT (pmol/l)*	**298**	**(279-318)**	**329**	**(318-341)**	**0.008**
LH (IU/l)	**5.7**	**(5.3-6.2)**	**4.5**	**(4.3-4.8)**	**<0.001**
FSH (IU/l)	4.9	(4.3-5.6)	4.3	(3.8-4.7)	0.082
SHBG (nmol/l)	38	(35-42)	37	(34-39)	0.359
E2 (pmol/l)*	80.0	(72.8-87.2)	87.1	(82.8-91.5)	0.098
E2/SHBG ratio*	**2.3**	**(1.9-2.7)**	**2.9**	**(2.6-3.1)**	**0.013**
E2/TT ratio*	5.3	(4.8-5.9)	5.7	(5.3-6.0)	0.254

*Additionally adjusted for current smoking. TT, total testosterone; cFT, calculated free testosterone; LH, luteinizing hormone; FSH, follicle stimulating hormone; SHBG, sex hormone binding globulin; E2; estradiol

Total E2 was lower in the fracture group although not reaching statistical significance. E2/SHBG-ratio was 21% lower in the fracture group when compared to controls (p=0.013). When men were categorised as having total E2 below or above the <73 pmol/l threshold, a higher proportion of the fracture group had low E2 (48% vs 35%, p=0.044), see figure 19.

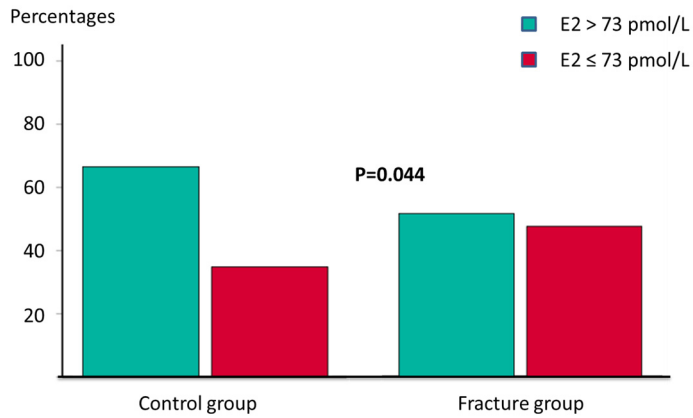


Figure 19. Proportion of males in the fracture and control group with total E2 levels below 73 pmol/l.

LH was almost 30% higher in the fracture group (5.7 vs 4.6; p<0.001) and there was a tendency towards higher FSH. No difference was seen in E2/TT-ratio between the groups.

Conclusion

In this study, to our knowledge the first specifically in young men with distal radius fracture exploring sex hormone levels, we find that men with fracture have lower estradiol, lower free testosterone and higher luteinizing hormone. Estradiol is a strong determinant of bone mass not just in women, but also in men; hence, the low levels of estradiol may be contributing to the observed lower BMD.

Paper III - Patient-related Outcome, Fracture Displacement and Bone Mineral Density following distal radius fracture in Young and Older Men

Background

The consequence following any osteoporosis-related fracture ranges from complete restoration of function to severe incapacitation. These aspects are also relevant for distal radius fractures, where higher age and osteoporosis are associated with increased fracture severity and often, a higher degree of fracture instability.

In older individuals, displacement does not necessarily translate into higher degree of disability, but evidence is conflicting and there is still no consensus. This study takes a different approach in investigating how patient-related outcome during the first year after distal radius fracture differs with age and whether post-fracture disability is associated with radiographic fracture properties, BMD and future fracture risk.

Patients and Methods

In this prospective cohort study, participants in the prospective arm, who had been followed the first year after fracture, were included. Men were categorized as younger (<65) and older (65+). Main outcome was DASH (Disability of the Arm, Shoulder and Hand) at 6-8 weeks and 12 months; poor outcome was defined as DASH >15. Fractures were classified according to AO´s 3 main types. Radiographic displacement (dorsal tilt >10° and/or ulnar variance >2mm) at initial presentation and at follow up 7-10 days later was recorded. BMD was measured by DXA and osteoporosis was defined as T-score ≤ -2.5 SD at any site measured. Using FRAX with BMD, 10-year probability of major osteoporotic fracture (MOF) and hip fracture were calculated.

Results

A higher proportion of older men had displaced fractures, particularly at follow-up (14/34 compared to 7/87 in younger men, p<0.001) and this was irrespective of treatment method (cast 5/18 vs 4/48 p=0.063; closed reduction and cast 3/8 vs 1/21 p=0.052; surgery 6/8 vs 2/23 p<0.001).

Disability one year after fracture was higher in older compared to younger men (median DASH 10 vs 2; p=0.002). Almost 50% of older men compared to 14% in younger men had a poor outcome, p<0.001. However, fracture displacement at follow-up was not associated with DASH score in older men (p=0.466).

Overall, BMD at femoral neck did not differ in those with undisplaced or displaced fracture at follow-up (unchanged by adjustment for age and CCI) and presence of osteoporosis was proportionally similar regardless of fracture displacement (21%). Osteoporosis did not significantly increase the risk of a poor outcome, DASH >15 (OR 2.39, 95% CI: 0.86-6.64). Neither was BMD associated with one-year DASH score in multiple regression analysis including age, treatment method, complications, radiographic parameters and CCI in the model.

Table 5. Patient-, fracture- and bone related factors in older men (≥65 years) according to fracture status at initial presentation

	Initial presentation		
	Undisplaced fracture	**Displaced fracture**	
	n=15	*n*=15	*p*-value
Age (years)	75 (6)	76 (5)	0.613
Charlson Comorbidity Index	2 (1;3)	2 (1;4)	0.152
No. needing surgery	0	6	
No. with major complication	0	2	
BMD femoral neck (g/cm^2)	0.864 (0.14)	0.806 (0.11)	0.239
FRAX score (median, IQR)			
Risk osteoporotic fracture	7.9 (6.3;13)	14 (8;21)	0.067
Risk Hip fracture	2.9 (1.6;6.9)	5.7 (2.9;13)	0.093
DASH score (median, IQR)			
6-8 weeks	18 (6;33)	45 (14;73)	0.024
12 months	6 (1;22)	30 (7;74)	0.035

Older men with displaced fracture at *initial* presentation had higher DASH at both 6-8 weeks and at 12 months; the higher DASH score was independent of the fracture being undisplaced or displaced after treatment at the latest examination (table 5). We also found a tendency towards higher FRAX risk in those with displaced fracture at the initial presentation (14% vs 8%) despite no differences in age, CCI or BMD.

Conclusion

Men over the age of 65 with distal radius fracture are more likely to have displaced fractures at both initial presentation and at follow up and higher degree of disability independent of radiographic appearance at follow up. BMD per se was not related to displacement or disability; however, most older men initially presenting with a displaced fracture also had unacceptable reduction at follow-up and higher future fracture risk, indicative of poorer bone quality.

Paper IV - Disability and pain are the best predictors of sick leave after a distal radius fracture in men

Background

Distal radius fracture often compromises working ability because of pain and inability to perform usual tasks of daily work. Due to the high incidence of distal radius fracture, many individuals are affected, therefore this fracture leads to many days lost from work in society as a whole and thus a large socioeconomic cost. Despite this fact, the factors determining length of sick leave after distal radius factor are very little studied; particularly among men. This study therefore describes sick leave in men with distal radius fracture, specifically exploring the impact of patient- and fracture-related factors.

Patients and Method

We included the professionally active men aged 20-65 with distal radius fracture from the prospective arm in this study (n=88). Potential factors affecting sick leave analysed in this study included treatment method, radiographic parameters pre/post treatment, complications, health, lifestyle and occupational demand. Patient outcomes were self-reported sick leave; DASH score; pain on a 5 likert scale; SF-36: Physical Component Scale (PCS) and Mental Component Scale (MCS). Sick leave was analysed in three clinically relevant groups: 'short' 0-6 weeks (immobilization and two weeks rehabilitation), 'intermediate' 7-12 weeks (allowing for longer rehabilitation) and 'prolonged sick leave' ≥13 weeks.

Results

Figure 20 shows the distribution of sick leave among the participants which ranged from 0 to 52 weeks (median 4; (IQR 0; 8); mean 6 SD 9).

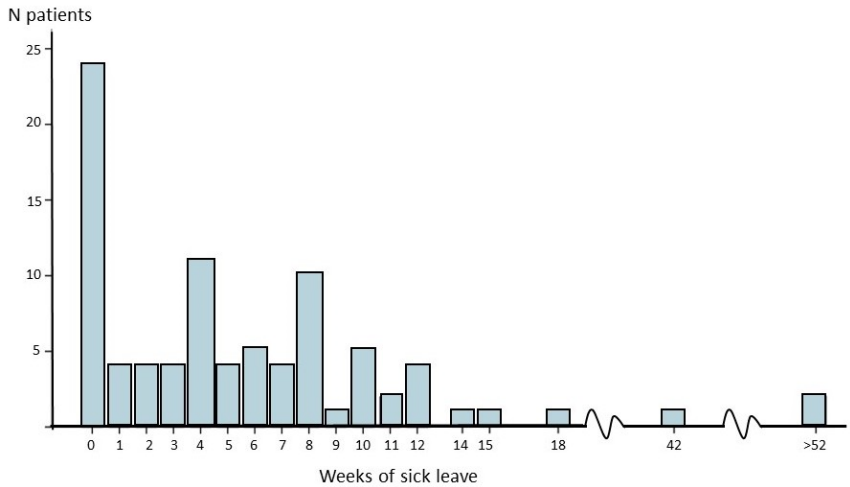


Figure 20. Distribution of weeks of sick leave after distal radius fracture in men

Within the three sick leave categories, we found that men with the longest sick leave had higher DASH scores and lower PCS at all time-points, although all three groups improved over time. The DASH score at one week was 22 points higher in those with prolonged sick leave compared to those with short (p=0.001(figure 21) and PCS was significantly lower.

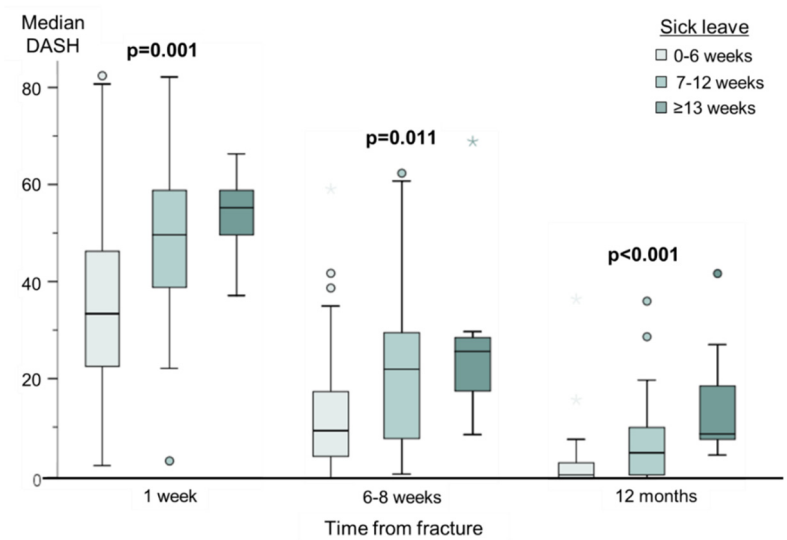


Figure 21. Self-reported disability (DASH score) at 1 week, 6-8 weeks and 12 months by sick leave category. Reported values are median DASH score and 95% confidence intervals.

Significant correlations between length of sick leave and DASH score, intensity of pain and PCS were apparent already at one week after fracture. The correlation between sick leave and pain was even stronger analysing treatment groups separately (closed reduction and cast r^s=0.56, p=0.007, surgery r^s=0.42, p=0.04). Conventionally evaluated factors e.g. treatment method and radiographic measurements generally showed weaker association to length of sick leave.

Conclusion

Although duration of sick leave is highly variable, we conclude that men of working age with distal radius fracture, who have higher self-reported disability and pain, as early as one-week after fracture, have longer sick leave, whether treated non-surgically or surgically.

Discussion

Bone mass in men with distal radius fracture

In this study, we investigated BMD in men with distal radius fracture, from the young adulthood to the old and we included fractures from all types of trauma. The main finding is that already from the age of 40 men have significantly reduced bone mass when compared to the background population. We found no difference in BMD between those with high or low energy fractures. Our results also revealed that three times more men with distal radius fracture have osteoporosis by definition compared to the background population.

The first study investigating bone mass in men with distal radius fracture by Tuck et al. was published in 2002 [130]. In 67 British men included, aged 40-80 years, they found as many as 42% of the fracture group to be osteoporotic compared with 10% in healthy age-matched controls. Our study did not confirm this very high prevalence as we found T-scores ≤ -2.5 in 17% in those 40-64 years old and 23% in those 65 years and above. The higher prevalence in the study by Tuck might be explained by the fact, that as many as 50% reported risk factors associated with secondary osteoporosis, compared to 21% in our study. This difference could also be explained by geographical differences in health, but discrepancies in reporting the risk factors of secondary osteoporosis cannot be excluded, even if the listed risk factors was similar. Others have found prevalence of osteoporosis to be 23% to 33% in men with low energy distal radius fracture from the age of 50 [131,132]. Measuring heal BMD, 44% of men above the age of 60 with the distal radius fracture from the same region as our study, had T-scores≤-2.5 [133]. Our result support the previous finding of Tuck of no difference in BMD between low and high energy trauma fractures. The high energy subgroup was small (n=24) which raised uncertainties concerning this finding; as our study was larger (n=91) we believe that the trauma level is largely irrelevant when evaluating risk of low BMD in men with distal radius fracture.

Men and women are different in their bone geometry and bone microarchitecture by means of evolution; thousands of years ago, males had physically more demanding duties like hunting and women raised the children and took care of the home and the

skeletons of men and women adapted. Society has changed a lot since the stone age, but the male skeleton is nevertheless built for heavier load and strain and men, in many cases, still do heavier work and activities compared to women (authors own observation). This is also illustrated by the fact, that men usually experience higher degree of trauma compared to women regardless of age [87]. Then low energy trauma in a woman might not be equal to low energy trauma in a man? The occurrence of a fracture with higher energy of trauma in a male (of course excluding traffic accidents and falling of buildings) may be a sign of impaired bone integrity and strength.

We found that men below 40 years with distal radius fracture show a tendency towards lower BMD. Previous studies have all excluded men below the age of forty under the assumption that younger men have a very low risk of osteoporosis and because most fractures result from higher trauma [80]. We included all distal radius fractures regardless of trauma level, based on our hypothesis that even men whose distal radius fracture resulted from moderate or high energy trauma may have impaired bone strength. Despite a possible higher level of trauma, it cannot be precluded that compromised bone strength is contributing to these fractures in men, as indicated by a higher prevalence of osteoporosis also in those below 40.

The distal radius fracture is located in the metaphysis, an area of long bones characterized by a large proportion of cancellous bone and lesser cortical thickness compared to the diaphysis, also in men. As such, the metaphysis is more vulnerable to the cortical thinning and deterioration of trabeculae observed with bone resorption [134], which occurs throughout the entire skeleton. It becomes obvious why the distal radius fracture is the earliest sign of impaired bone strength. It also means compromised bone quality may contribute to other appendicular fractures in men.

The studies above, including our own, all used male reference data when calculating T-scores. The present recommendation is using female reference data due to the assumption that men and women fracture at the same absolute BMD value [121]. We used male reference values to enable comparison with the previous studies, but we also included T-scores derived from female reference data as recommended by the International Osteoporosis Foundation, which as expected resulted in a lower proportion diagnosed as osteopenic and osteoporotic in both fracture and control groups. The fact still remains, that men with radius fracture have a demonstrably lower bone mass compared to the background population.

Bearing the impact of the bone mechanical properties of men in mind, using the female reference data might be correct when diagnosing men with osteoporosis using DXA. However, the question arises, when do impaired bone strength become an illness in a

male? When he fractures during his normal daily living or when he fractures during less heavy activities?

Sex hormones in young men with distal radius fracture

Younger men have not previously been considered a risk group, primarily because younger men have more high energy traumas and but also because men in general are not considered at risk of osteoporosis. One of the most interesting findings of the previous study, was an increasing prevalence of men with T-scores ≤ -2.5 with age, which implies a greater bone loss in this population, figure 22.

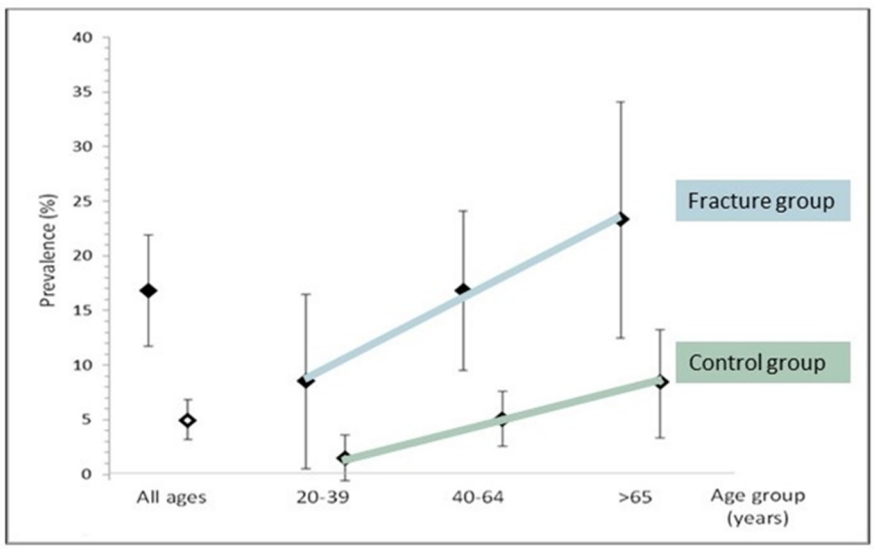


Figure 22. Increasing propoprtion of men with T-score≤-2.5 in men with distal radius fracture with age compared to controls

This suggests an underlying pathology in men with distal radius fracture causing a higher bone loss. The association between low bone density and fracture needed to be further studied in this age group to elucidate possible underlying causes of the observation. The crucial impact of sex hormones, and in particular estradiol, on peak bone mass and on BMD in older men is quite well established, but with a missing link concerning lack of knowledge about younger men with fracture.

In this case-control, cross-sectional study, we therefore investigated sex hormone profiles of younger men with distal radius fracture. Our results showed that a higher

proportion of fractured men aged 20 to 50 had low levels of both calculated free estradiol and testosterone when compared to population-based age-matched controls. The concurrent elevated LH, as an indication of increased hypothalamic drive on the testes, suggests a testicular deficiency, for reasons unknown, as a possible cause of the observed lower levels of testosterone and estradiol.

One study has analysed men with radius fracture and sex hormones [135]. Although smaller (n=39), only including men above 70 with low energy fractures and only measuring testosterone, the conclusion was largely similar to ours. Of note, while bioavailable testosterone among fracture cases compared to controls was 16% lower in these older men, in our cohort, cFT was already 10% lower in these young to middle-aged men.

In contrast to the published literature, we did not find an association between BMD and levels of testosterone or estradiol in younger men, although possibly due to the comparably small cohort size. However, we speculate that the effect of low sex hormones levels on bone density may not yet have manifested on an individual basis but only on a group level, while it is possible that bone micro-architectural properties are affected. By means of pQCT, peripheral Quantitative Computed Tomography, the three-dimensional macro- and microstructure of both the cortical and trabecular bone can be investigated in detail [136], which would have been interesting to study.

A cross-sectional study cannot show causative relationships. Even though we do not find a statistically significant association between sex hormone levels and BMD, there is biological plausibility since we have a group of younger men with fracture, who have lower BMD *and* low levels of free testosterone and estradiol. Based on the actions of estradiol, both on the growing and on the older skeleton, our study implies that a distal radius fracture may be the first sign of of subnormal levels of sex hormones resulting in impaired bone strength in men. However, reverse causation, meaning that a disorder in the skeleton is causing lower levels of testosterone and estradiol, must also be considered possible. Especially in the light of recent studies, revealing that osteocalcin, a hormone produced by osteoblasts, induces testosterone production in Leydig cells of the testes in both *ex vivo* and *in vivo* studies [137]. Thus, a disturbance somewhere on the osteocalcin pathway from the osteoblast to the receptor in the Leydig cells would cause lower levels of circulating testosterone and thus less substrate for estradiol, and as a consequence lower BMD and impaired bone strength.

It would have been most optimal to investigate sex hormones also in the older men; however, it was not possible in the present study as the biochemical analysis from the older controls was not available to us. A future larger study is warranted; a study across

a broad range of ages investigating the impact of low hormone levels on BMD and in particular, how and when the effect is seen.

Determinants of outcome and the influence of age

The aim of the third study was to explore association between bone integrity and age on fracture severity and patient-reported outcome after a distal radius fracture. We found that older men more often had a higher degree of disability and that displaced fractures were more common; but despite this, in the entire group of older men, displacement at follow-up was not associated with patient reported outcome. This indicates that, the patient-reported outcome is the same regardless of how the fracture looks radiographically. This is supported by several studies in patients older than 60 years, reporting higher DASH scores in elderly [81,97], higher degree of instability [138] and that radiographic appearance does not affect patient reported functional outcome [99,139–141]. Even studies with older patients with higher activity level, when scored on a physical activity questionnaire, have not been able to show an association between displacement and higher degree of disability [99,100]. On the other hand, a recently published randomised study showed, that elderly above 70 years with displaced fractures at the initial presentation had better range of motion and DASH-scores, both in short and long term, when treated with a volar locking plate compared to closed reduction and splinting [142].

We found that elderly men with undisplaced fracture at the initial presentation, report minor degree of disability one year after fracture. In our study, following our standard treatment protocol, the latest x-ray examination is 2 weeks after fracture if no other indication has arised. It has been shown, that one third of fractures that are undisplaced both initially and at the weekly follow-up, may displace later [108]; thus, probably more fractures in in this subgroup have healed with unacceptable radiographic appearance but still with a good self-reported outcome. This implies that those with acceptable fracture appearance at initial presentation in general have a good final result.

But this doesn't mean that all elderly patients do well after a distal radius fracture. One of the most interesting findings in our study is that most of the elderly with displaced fracture at initial presentation also had displaced fracture at follow up and reported worse DASH scores at 1 year independent of fracture appearance at the 2-week follow-up, figure 23. This group of older men also have tendency towards higher risk for future major osteoporotic fracture.

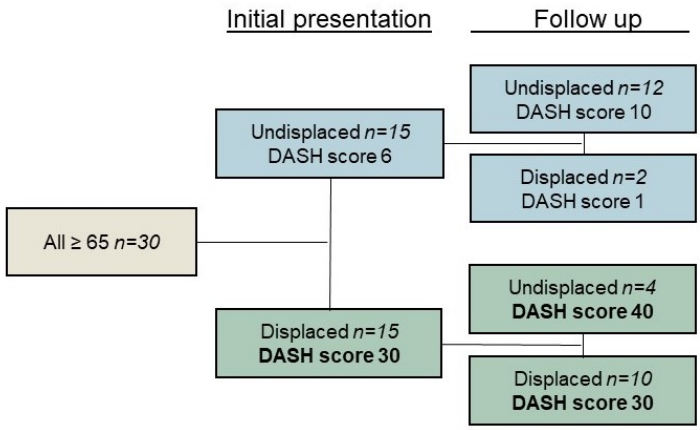


Figure 23. Flow chart illustrating older men and their fracture staus at initial presentation, at follow up and the median DASH score at 1 year showing higher DASH score in those with displaced fractures at initial presentation.

This suggests that an initial displacement at fracture occurrence is not only critical to the final result, it also indicates a higher degree of fracture instability and concomitant poorer bone quality, probably due to higher biological age or frailty. In elderly and frail low demand patients, closed reduction has been shown to fail in almost all displaced fractures, either primarily or during the following weeks of immobilisation in plaster [(143)] and risk of displacement is found to be fifty percent at the age of 58, increasing to seventy-seven percent in 80-year olds [(144)]. Since recent studies have shown better self-reported outcome if elderly with displaced fractures are treated with surgery (volar locking plate) compared to closed reduction [(142,145)], our result indicate, that surgery should be considered in an early stage. All elderly in our study who very treated surgically had an external fixator. It may be that our results would have been different, had they been treated with volar locking plates, which have somewhat better radiographic outcome compared to external fixator [(104)].

If it is true that the radiographic appearance does not affect self-reported outcome in the elderly, then why did we find such a large difference in DASH scores between those with and without displacement at the initial presentation? It may be an expression of the patients pre-existing functional status, as DASH score increases with higher age and presumably also with higher biological age and frailty [(146)]; having the DASH questionnaire at baseline as measure of functional status before fracture would have been valuable in our study. Those with higher degree of pre-fracture disability may be more fragile and their fractures more prone to instability. This is supported by the fact, that those with displaced fracture at the initial presentation had higher FRAX risks. Finally, patients with displaced fracture and high biological age, are generally not as

often treated surgically or reduced as vigorously as their more vital peers, due to the assumption that it does not benefit them.

Age has an impact on fracture appearance and disability measured by DASH in men, but in the present study, low BMD corresponding to osteoporosis was not associated with patient-related functional outcome one year after fracture. This contrasts with postmenopausal women, where osteoporosis negatively impacted DASH-score independent of fracture appearance and comorbidities [147], although this association is far from universal [148,149]. Possibly, the association is obscured in our study by the relatively low number of men with osteoporosis; nevertheless, directionally the trend indicates a higher risk and larger studies are required before definitive conclusions can be made.

Sick leave after distal radius fracture in men

In this prospective cohort study, we investigated sick leave after acute distal radius fracture and followed the men one year after fracture. We found that sick leave after a distal radius fracture in men is highly variable; while almost one quarter return to work almost immediately without requiring any sick leave, a few are unable to return to work even after 12 months.

Comparing to the previous study by MacDermid [116], we found large differences in length of sick leave; a median eight weeks compared to only four weeks in our male only cohort. Another difference is in the self-reported outcome; albeit not using exactly the same sick leave categories and uncertainty whether mean or median DASH scores are reported, participants in the MacDermid study exhibited much higher degree of disability. This finding might be skewed by including women as women have higher DASH compared to men [97] or if the participants in the Macdermid study had more severe fractures. Differences in social insurance systems could also affect length of sick leave. However, both studies share the main conclusions: that approximately twenty percent do not lose any time off work and that self-reported disability is the strongest predictor of length of sick leave.

A finding of great importance is that higher disability and pain intensity as early as one week after a distal radius fracture, is a risk factor for longer sick leave in men, whether treated non-surgically or surgically. The importance of the patients perception of level of pain is obvious in both bivariate and multiple regression analyses and the finding is supported by an earlier study, showing that baseline pain intensity predicts chronic pain in both men and women with distal radius fracture [150]. Subjective pain level during

the first weeks after fracture has proven to be the most important factor to predict a high DASH score at one year, followed by comorbidity, education level and coping [151].

"Pain" is a subjective symptom; it is multifactorial involving both injury (fracture severity, treatment, complications) and patient related factors (age, educational level, prior pain experience and psychosocial factors) [152]. Not many of these factors are modifiable but some are, in particular *present* pain experience and coping mechanisms. By identifying risk factors leading to chronic musculoskeletal pain following an acute injury, we may minimize the risk of persistent pain, disability and prolonged sick leave.

The following question is then: how can we help patients experiencing high levels of pain besides prescribing pain medication? There is still no consensus on the most appropriate rehabilitation program following a distal radius fracture in adults, for example, supervised therapy versus a home exercise program [153] and current recommendations emphasize the need for clinicians to rely on their experience and clinical judgement [154]. Based on our study and the fact that both self-reported outcome and chronic pain at one year is mostly affected by higher degree of pain early after fracture, we believe that pain should act as a yellow flag assisting the clinician in allocating rehabilitation resources and other pain-reducing treatment.

Clinical implications

Men are generally forgotten in studies of distal radius fracture and osteoporosis. This highlights the importance of this thesis in terms of understanding patterns of fragility fracture risk in men. For males, having a distal radius fracture and probably other appendicular fractures, regardless of how it occurred, implies compromised bone strength and men constitute a group that are at higher risk of future fractures.

Osteoporosis almost always leads to decreased bone strength and bone fragility. On the other hand, bone fragility is not always caused just by osteoporosis. Having a fracture could be a symptom of an underlying and perhaps undiagnosed illness and even as orthopaedic surgeons we need to have a holistic approach to our fracture patients, including the males, to capture unrecognized causes of fracture. Our result show that low levels of sex hormones might be one of those undetected conditions. The question is how this should be addressed and whether androgen replacement should be recommended to these individuals. There is no published randomized placebo-controlled trial, but available data points to an increase in BMD with such therapy in sub fertile men [155].

Compared to women, only a small proportion of men at risk of osteoporosis are evaluated and receive treatment. I hope that this thesis will raise awareness of the higher prevalence of osteoporosis in men, not only men with distal radius fracture but men with all fractures. Both clinicians and the general population need to be aware that osteoporosis in men *is not* uncommon. By identifying men at risk of not only the second fragility fracture but also *the first*, we may prevent major fractures such as hip fracture, which in men causes higher mortality than in women.

As to the elderly with distal radius fracture, we are still in the mist with no clear answers. Although some studies show that in elderly radiographic appearance to not correlate with self-reported outcome, this does not mean that all elderly do well after distal radius fracture. In the study by Anzarut [99], which included elderly who lived independently, the emphasis is on the 50-60% who were satisfied with the final result. But what about the 40% who were dissatisfied? We need to be able to identify the negative predictors of self-reported outcome in elderly and this thesis demonstrates that a displaced fracture at initial presentation probably is one of those predictors. The question still remains what the best treatment is for these patients. The elderly patients' physiologic and actual ages may vary greatly and perhaps be even unrelated to their perceived youth. I believe, we need to consider the potential separation between actual, physiologic, and perceived age when managing distal radius fractures in the elderly.

We are facing a growing number of distal radius fracture in the working population. The consequence will be a larger demand on our health care system and a greater socio-economic cost. The results from this thesis lead us to believe that we can identify individuals at risk of long sick leave by the intensity of pain early after fracture. The following question is what measures that should be taken to reduce pain levels. As no evidence exists regarding rehabilitation programs after distal radius fracture, I believe, the first step to address high levels of pain should be closer follow up´s at the physiotherapist in addition to pain medication.

This thesis illustrates the many aspects of fracture treatment and orthopaedic surgery. Treating the fracture is the easy part. However, we need to treat *the patient* and that is much more complicated. Hopefully, I will gain wisdom in the future.

Methodological considerations

We have performed the largest comparative study of BMD and sex hormones in men with distal radius fracture against a background population. We have covered the full spectrum of ages and also specifically investigated the often-overlooked group of

younger men below the age of forty. These are major strengths of this work. However, as every other study, it also has some weaknesses.

The overall response rate was 40%. On the other hand, our participation rate is similar to equivalent osteoporosis studies, but different from mail-based studies focusing only on self-reported outcome [81,132] with physical participation being more demanding than returning questionnaires. Furthermore, studies in men often have lower participation rates [81,132,156]. There was no difference in age distribution between participants and non-participants, but as a cohort study there is always risk of selection bias.

The risk of selection bias also pertains to the controls. They may attend both because they are healthier or less healthy depending on reason for agreeing to participate, which is inherent to most studies. The fact that the controls were not specifically collected for the present study, lead to that some variables of importance of fracture occurrence, such as the risk of falls, family history of osteoporosis, could not be included in the analysis. We recognize the limitation in not being able to take these confounding factors into account. The prevalence of distal radius fracture among the controls at the time of recruitment is not known; excluding controls with previous distal radius fractures would, however, most likely enhance the differences in both BMD and sex hormones.

Selection bias can affect the external validity of a study. With perfect external validity, the results from this thesis would be absolutely applicable to all men with distal radius fracture living in south of Sweden today. In a study of osteoporosis, that is utopia. Considering the fact, that the really large osteoporosis study MrOs has participation rates between 10-15% [157], our study has acceptable attending rates. Although the present study is one of the largest of men with distal radius fracture, it may in some instances be underpowered to detect significant differences. Since the incidence of distal radius fracture in men is comparably low, it would require an extremely long inclusion period to reach the number of participants as in the above-mentioned study. An alternative design would have been a registry study, which allows for inclusion of most individuals with a certain condition. However, the longitudinal design of the present study has the advantage of studying detailed aspects of distal radius fracture in men, which would not have been possible with a registry study.

Paper I

The inclusion period was long but is unlikely to affect the results as homogeneous environment and personnel were maintained throughout. While a fracture occasion can lead to a lifestyle change altering osteoporosis risk, we consider this unlikely since only two variables (BMI and oral steroid use) differed between the retro- and prospective arms of the study while BMD and sex hormones was similar for both.

Paper II

The unstandardized blood sampling with respect to diurnal variation and food intake and the single sample collection are obvious weaknesses of the study. We compensated for this by performing adjustments for time-of-sampling. We believe, that, the fact that luteinizing hormone, which is not subject to diurnal variation, was significantly higher in the fracture cases supports our finding of lower testosterone and estradiol in the fracture group. In longitudinal studies, changes in methods of analysis during the course of study is often encountered and we were not spared.

Serum samples was handled accurately according to standard procedure at our lab and had not undergone any freeze-thaw cycles. While testosterone and estradiol are stable during extended storage, SHBG levels may change slightly with time in storage. We also adjusted for the potential effect of evaporation due to storage time (which was minimal) and we do not believe this influenced the results.

Paper III and IV

There might be bias towards higher DASH scores, since non-responders to DASH questionnaire at one-year evaluation were younger and with less severe fracture types, a patient category usually experiencing better functional outcome.

We did not have objective functional measurements such as range of motion or grip strength, which could have been valuable. On the other hand, these variables have not shown to clearly correlate with disability in terms of DASH scores [110].

Our sick leave data was self-reported, which may not fully agree with administrative data [158,159]. Recall bias can be expected, but we believe that the continuous follow-up reduces such impact.

Conclusions

In this thesis, investigating bone mass and patient-related outcome in men with distal radius fracture in men, from working age to the oldest, we come to the following conclusions:

- Men with distal radius fracture have lower BMD, regardless of level of trauma, which was observed even in the younger men. It is apparent that also men with distal radius fracture and probably other appendicular fractures are at increased risk of skeletal fragility.
- Younger men with distal radius fracture have lower BMD *and* lower free estradiol and testosterone. An altered sex hormone profile at young age may be a cause of skeletal fragility in older age.
- Older men with distal radius fracture are more likely to have post-fracture disability compared to younger men. Especially older men with a displaced fracture at the initial presentation have worse self-reported outcome and also a higher risk of future fracture. However, BMD was not associated with disability or displacement.
- In men of working age with distal radius fracture, higher self-perceived disability and pain as early as one week after fracture are the strongest predictor of length of sick leave, regardless of treatment type. Preventive strategies are called upon to reduce the burden for both the individual and society.

Future perspectives

I have discovered and learned countless things during my time as a PhD student, but the one thing that becomes obvious time after time is: When you find the answer to one question, ten new are raised. Instead of a feeling of enlightenment, I feel there are so many further questions that need illumination.

In the most ideal of worlds with unlimited resources, I would conduct a very large longitudinal prospective cohort study following men from childhood to old age, assessed at 5- to 10-year intervals. The major focus would be to elucidate how sex hormones affect the skeleton during a lifetime; what comorbidities are associated with subnormal hormone levels and when do they become evident. My great grandchildren would do their thesis on that material. But since I´m not a billionaire philanthropist, a more realistic study would begin by performing pQCT on those men with distal radius fracture who have subnormal sex hormone levels, to determine how the bone microarchitecture is affected.

As an orthopaedic surgeon, I´m devoted to my patients and the clinical work. And the distal radius fracture has intrigued me, especially those occurring in the elderly. Based on my studies, I believe that we need to investigate to a much greater extent the elderly with displaced fractures. In an ongoing and unpublished study at our orthopaedic department, one third of patients above the age of eighty report DASH scores above 35 which, given that >15 is considered 'poor', translates as major disability. Obviously, we are not giving this patient category the appropriate treatment or follow-up care. In light of the growing elderly population, the number of over 65's suffering a distal radius fracture will increase by more than 50% by 2050 [88] and the prospect of leaving so many affected individuals with major disability is unacceptable.

We need new tools to better discriminate between those elderly who would benefit from surgery, perhaps an activity score, taking the patient's own perceived function into account.

As DASH score, naturally, increases with age, I don't believe that it adequately captures the elderly patient's perception of wrist function after distal radius fracture. I like to keep things simple and would ask the following question in the emergency ward and one year later: On a visual analogue scale 0-10, "How satisfied are you with your wrist

function?". Having an age-related decreased function is the norm for most elderly and they are often satisfied with that; however, the DASH score would turn out high as in higher disability. I also believe elderly are more inclined to accept disability after a fracture. That is why I think, that asking for "satisfaction" would be a relevant measure in addition to the DASH score in future studies of distal radius fracture in the elderly.

As higher level of pain early after fracture is a major determinant of self-reported outcome and sick leave at one year after fracture, would a more aggressive rehabilitation program be beneficial? I would like to see more randomized studies on rehabilitation after distal radius fracture to elucidate what rehabilitation program is best for which patient group. In this interactive age and in a society with limited health care resources, I believe that an app could do much of the job by guiding the patient in the rehabilitation and also pin out those, who need to see a physiotherapist more regularly.

Don't worry, I´ll be busy…

Acknowledgements

First of all, I would like to thank all of the men, who took their time to participate in this study, "MANRAD". You have shared valuable information and contributed greatly to research. Thank you, Karin Önnby, for collecting all the data.

Kristina, my supervisor, you are the essence of research. Sharp, honest albeit diplomatic, patient and with a great sweet tooth. Thank you for giving me a magnificent education.

My co-supervisor Fiona, you are my big sister in research. You encouraged me when I was down, pointed me in right directions when I was off track and you taught me the art of "tweaking". I now know that sweets are obligatory when writing articles, so are gin and tonic in transatlantic flights.

To all my colleagues at the orthopaedic department and especially to my girls in "Pigkammaren". Thanks for all the laughter and tears, our roof has no limit. I will try to keep my desk a bit tidier from now on. A special thanks to Daniel Jerrhag, you have been my rock and my shoulder to cry on.

Celinda, my fellow student and dearest friend. Although we´re 300 km apart, you are always right next to me in times of need. Thank you for craziness, stubbornness and for giving me perspective.

My real big sister Åsa, and my brother Ulle. Thank you for always being there for me. You are my safety net that never fails.

My father, Niels "Daddy". Finally, I completed the thesis! You may call me MD PhD Egund Junior. Thank you for all your patience, support and love.

My mother, Erny "Mams". Thank you for putting up with me. You are my mother, my best friend and my partner in crime. I am, who I am, because of you.

And finally, to my sons Jack and Max, thank you for your unconditional love, your wonderful hugs and for putting up with every "just a minute". Without you in my life, I would be nothing. Because

> *"You are my sunshine, my only sunshine, you make me happy when skies are grey, let me tell you how much I love you, please don't take my sunshine away"*

Appendix I

Hormone arrays: Methods of analysis

Testosterone

Total testosterone (TT) was assessed by a two-step competition assay with ElectroChemiLuminiscenceImmunoassay (ECLI) detection technique (Cobas, Roche Diagnostics). Analytic range 0,087–52,0 nmol/L, total coefficient of variation (CV) ranging from 7% at 3 nmol/L to 4% at 15 nmol/L). Reference range men ≤ 50 years 5.0-30 nmol/L.

Estradiol

Total estradiol (E2) was measured with liquid chromatography-tandem mass spectrometry method mass-spectrometry (LC-MS/MS, SCIEX, Massachusetts USA). Analytic range 6–600 pmol/L, total CV ranging from 8.9% at 16.9 pmol/L to 4.7% at 104.8 pmol/L). Reference range men 37-147 pmol/L.

Luteinizing hormone

Luteinizing hormone (LH) was determined with a one-step immunometric sandwich assay with ECLI detection technique (Cobas, Roche). Analytic range 0.10–200 IE/L, CV ranging from 3% at 5.0 IE/L to 2% at 37 IE/L). Reference range men 1.7-8.6 IE/L.

Sex hormone binding globulin

Sex hormone binding globulin (SHBG) was assessed with a one-step immunometric sandwich assay with ECLI detection technique (Cobas, Roche). Analytic range 0.35–200 nmol/L, total CV 3% at 25-53 nmol/L). Reference range men 10-80 nmol/L.

Follicle stimulating hormone

Follicle stimulating hormone (FSH) was determined with a one-step immunometric sandwich assay with ECLI detection technique (Cobas, Roche; analytic range 0.10–200 IE/L, total CV 3% at 5.0-41 IE/L). Reference range men 1.5-13 IE/L.

Appendix II

Analysis of estradiol

For all fracture cases E2 was measured using LC-MS/MS. For controls, the less sensitive modified DELFIA had been used.

Serum from 30 of these 194 controls was available, and E2 was re-analysed using LC-MS/MS. Using linear regression to identify the conversion factor, as described above, all values obtained by the modified DELFIA were converted to LC-MS/MS equivalent values.

The regression curves, with linear curve equations and R^2 values, are presented in figure 24.

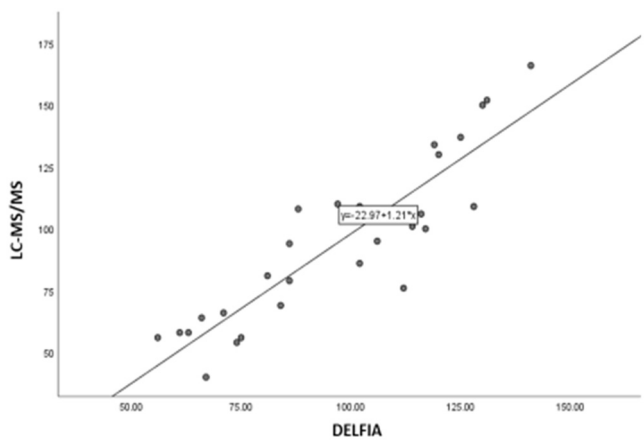


Figure 24. Internal validation plots for measurement of serum E2.
The line represents the linear curve of best fit and the corresponding conversion factor and R^2 are reported in the figure. Subjects with mean difference > ± 2SD from the average difference between the two methods were excluded from calculation. Mean difference and SD between methods was -5.53 (18.93).

Analysis of testosterone, LH, SHBG and FSH in controls

Approximately half of the controls (103/194) had already attended assessment (2010-2013), when the method of analysis for testosterone, LH, SHBG and FSH at the Dept. of Clinical Chemistry changed from Access sandwich immunoassays to Cobas ECLI (Roche). Serum from 46 of these 103 controls was available, with which we performed internal validation comparing both methods.

Using linear regression analysis and excluding subjects where the mean difference between the two methods differed > 2SD from the average/mean difference, we obtained a conversion factor from the linear curve of best fit. With these, all values obtained by the former sandwich immunoassays were converted to ECLI equivalent values.

The regression curves, with linear curve equations and R^2 values, are presented in figure 25 A-D.

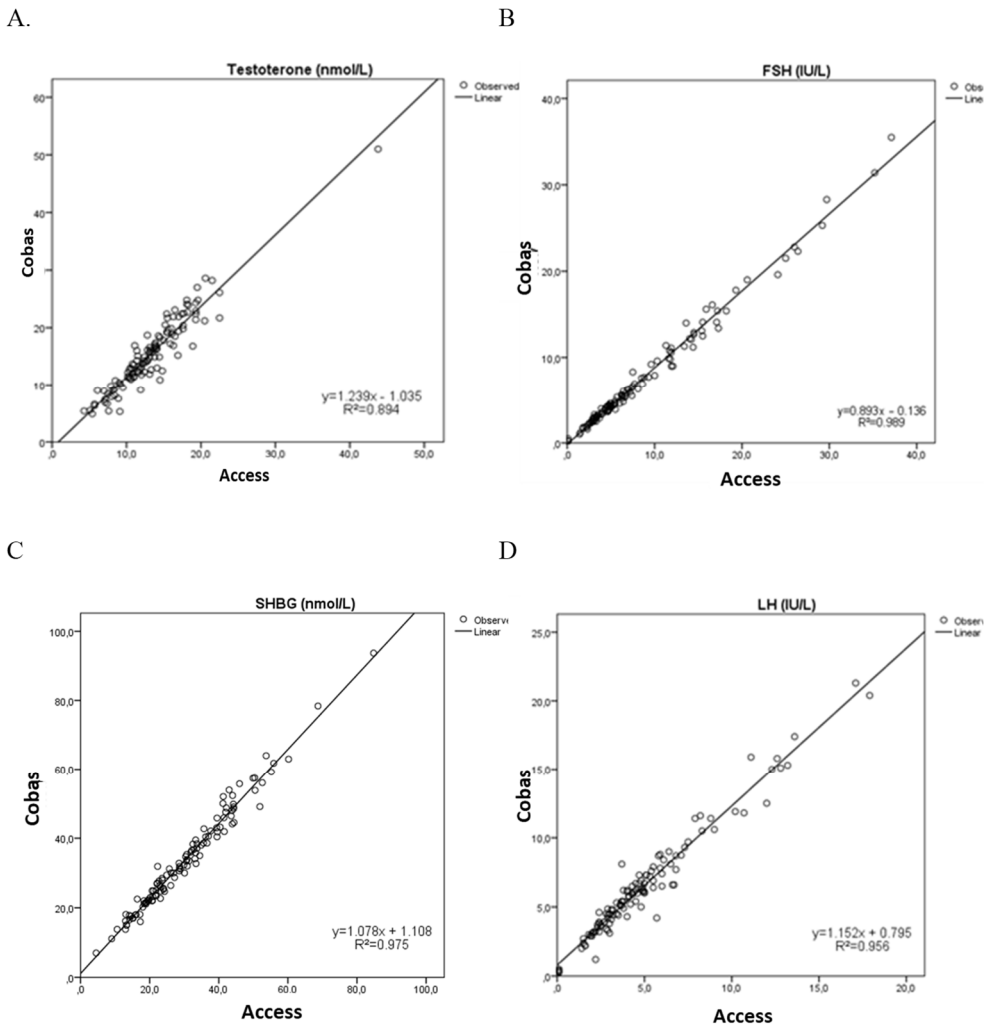


Figure 25 A-D. Internal validation plots for measurement of serum TT, SHBG, LH and FSH.
Lines represent the linear curves of best fit and the corresponding conversion factors and R^2 are reported in the figures. Subjects with mean difference >± 2SD from the average difference between the two methods were excluded from calculations.

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About the author

Lisa Egund born in 1978 received her medical degree at Copenhagen University in 2006. She started working at the Department of Orthopaedics at Skåne University Hospital, where she returned after doing her internship at Bornholm Hospital. During her residency in orthopaedic surgery she started the work of this doctoral thesis under supervision of Professor Kristina Åkesson. Lisa Egund received her qualification as specialist in orthopaedic surgery in 2017 and is currently working at the Trauma Section at Skåne University Hospital Malmö.

The distal radius fracture is the most common fracture of them all and it affects both men and women of all ages. However, no study had investigated men specifically. The overall aim of this thesis was to comprehensively study adult men with distal radius fracture addressing the bone mass of adult men from working age to the old and in addition, exploring determinants for self-reported outcome and sick leave.

In summary, our results show that in men, as in women, a distal radius fracture is a red flag for fracture management as they have markedly lower bone density. An altered sex hormone profile at young age may be a cause of skeletal fragility in older age. Therefore, men should be evaluated for osteoporosis as routine and sex hormones should also be considered. The treatment of older men with radius fracture needs further improvement, since many have disability 1 year after fracture. In men of working age with distal radius fracture, higher degree of pain as early as one week after fracture is the strongest is the greatest risk factor of longer sick leave, regardless of treatment type.

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