Low-energy fracture of the distal radius in middle-aged and elderly Norwegian women and men

Topics related to osteoporosis, fracture risk and vitamin D

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Scientific environment

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Contents

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Abstract

Introduction

Low-energy distal radius fractures normally occur earlier in life than hip and spine fractures and may be the first presentation of osteoporosis. Few studies have addressed the association between distal radius fracture and osteoporosis. Vitamin D inadequacy is associated with an increased risk of hip fractures, but the association with distal radius fractures has not been explored.

Aims

The aims of this study were to determine the prevalence of patients with a distal radius fracture in need of osteoporosis treatment according to certain guidelines, calculate the subsequent fracture risk, and to investigate the association between distal radius fracture and osteoporosis and vitamin D inadequacy.

Materials and methods

Paper I is a cross-sectional study of 1,576 female and 218 male distal radius fracture patients aged 50 years and older from Bergen, Kristiansand and Skien. Papers II and III are case-control studies based on the 664 female and 85 male patients from Bergen and 554 female and 54 male controls from the same area.

Bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (DXA). A self-administered questionnaire included information on health and lifestyle factors. A fracture risk assessment tool (FRAX®) was used to calculate the 10-year fracture risk. Serum 25-hydroxyvitamin D (s-25(OH)D) was analysed.

Results

The prevalence of T-score ≤ −2.0 and ≤ −2.5 standard deviation (SD) at femoral neck was 51% and 31% in female and 38% and 20% in male distal radius fracture patients, respectively (Paper I). The 10-year FRAX® estimated hip fracture risk in all female and male patients was 9% and 6%, respectively. The corresponding figures for female and male

patients with osteoporosis were 18% and 16%, respectively. A large proportion of distal radius fracture patients with a high 10-year fracture risk did not have osteoporosis.

In the matched case-control study (Paper II) the prevalence of osteoporosis was 34% in female patients compared to 10% in female controls. Among men the figures were 17% and 13%, respectively. After adjustment for confounding factors by conditional logistic regression, osteoporosis was significantly associated with distal radius fractures in both women and men.

The mean s-25(OH)D was 67 nmol/L in female patients and 79 nmol/L in female controls ($p<0.001$) (Paper III). In men the corresponding figures were 65 and 77 nmol/L ($p=0.017$), respectively. In adjusted conditional logistic regression analyses, s-25(OH)D < 50 nmol/L, and 50-75 nmol/L were associated with distal radius fractures in women, and s-25(OH)D < 50 nmol/L was associated with distal radius fractures in men.

Conclusions

A high proportion of the distal radius fracture patients had osteoporosis compared to matched controls. However, a large proportion of the patients were not diagnosed with osteoporosis, and many of them had a high FRAX® score without having osteoporosis. Furthermore, osteoporosis and vitamin D inadequacy were associated with distal radius fractures. Thus, our results indicate that patients aged 50 years and older with a low-energy distal radius fracture should be referred to bone densitometry for measurement of BMD, and be evaluated for potential risk factors, as well as for vitamin D inadequacy.

List of publications

Paper I

Øyen J, Gjesdal CG, Brudvik C, Hove LM, Apalset EM, Gulseth HC, Haugeberg G. **Low-energy distal radius fractures in middle-aged and elderly men and women - the burden of osteoporosis and fracture risk. A study of 1794 consecutive patients.** *Osteoporosis International 2010; 21:1257-1267*

Paper II

Øyen J, Brudvik C, Gjesdal CG, Tell GS, Lie SA, Hove LM. **Osteoporosis as a Risk Factor for Distal Radial Fractures: A Case-Control Study.** *The Journal of Bone and Joint Surgery American 2011; 93:348-356*

Paper III

Øyen J, Apalset EM, Gjesdal CG, Brudvik C, Lie SA, Hove LM. **Vitamin D inadequacy is associated with low-energy distal radius fractures: A case-control study.** *Bone 2011; Feb 2 [Epub ahead of print]*

Abbreviations

Bergen AED	Bergen Accident and Emergency Department
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence Interval
CV%	Coefficient of Variation in percent
DXA	Dual-energy X-ray Absorptiometry
FRAX®	Fracture Risk Assessment Tool
ESP	European Spine Phantom
HUH	Haukeland University Hospital
NHANES III	The Third National Health and Nutrition Examination Survey
NMA	Norwegian Medicines Agency
NICE	National Institute of Health and Clinical Excellence
OR	Odds Ratio
PTH	Parathyroid Hormone
SD	Standard Deviation
UK	United Kingdom
US	United States
WHO	World Health Organisation
$1.25(OH)_2D$	1.25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D

Definitions

Bias	A methodological error in the collection or interpretation of the data
Bone mass	The amount of bone tissue/minerals (mostly calcium and phosphorous) contained in a specific volume of bone
Bone mineral density	A measure of the density of bone
Bone densitometry	The quantitative assessment of bone mass
Confounding	The estimated effect of the exposure being mixed with the effect of a different factor
Epidemiology	The study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control of health problems
External validity	The extent to which results from a study can be generalised to other populations outside the study population (also called generalisability)
Information bias	Bias caused by wrong information about exposure and/or outcome caused by faulty methods for obtaining such information
Internal validity	The degree to which the estimated outcome or association between exposure and outcome is true or valid for the population of the study
Low-energy fracture	A fracture resulting from minimal trauma (e.g. falling from standing height or lower)
Osteoporosis	A disease characterised by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced skeletal fragility and increased risk of fractures[1]
Peak bone mass	The maximum amount of bone acquired at skeletal maturity.
Selection bias	Error due to systematic differences in characteristics between attendees and non-attendees in a study

T-score	The number of standard deviations above the mean of healthy young individuals at peak bone mass using a reference population
Z-score	The number of standard deviations above the mean of age- and sex-matched controls
1.25-dihydroxyvitamin D	An active vitamin D hormone, responsible for vitamin D action
25-hydroxyvitamin D	A circulating storage form of vitamin D; a measure of vitamin D status

1. Introduction

The distal radius fracture is the most common fracture type in both women and men[2, 3]. Every year approximately 15,000 adults suffer from a distal radius fracture in Norway[4]. A distal radius fracture occurs on average about 15 years earlier in life than a hip fracture[5]. Thus, a distal radius fracture may be the first presentation of osteoporosis. Osteoporosis is characterised by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced skeletal fragility and increased risk of fractures[1]. Hence, a good fracture prevention strategy might be to designate distal radius fracture patients as an intervention group, in order to detect and treat osteoporosis at an early stage. This might reduce the future risk of the adverse consequences of osteoporosis[5]. The increasing elderly population in Western society makes it likely that the number of osteoporotic fractures will increase among both men and women in the coming years[6]. Therefore, strategies to reduce the burden of osteoporotic fractures are essential[7]. Today, distal radius fracture patients are often not evaluated for possible osteoporosis[8-10]. This can be explained by the fact that some clinicians treating these patients do not link a fracture of the distal radius to osteoporosis, but rather to the fall mechanism. On the other hand, some clinicians believe all low-energy distal radius fractures in middle-aged and elderly patients are caused by osteoporosis and suggest drug treatment without the need of BMD measurements (Appendix 1). The guidelines from the Norwegian Medicines Agency (NMA) suggest treatment after a low-energy fracture and a T-score ≤ -2.0 standard deviation (SD)[11]. However, the prevalence of distal radius fracture patients in Norway with indication for osteoporosis treatment is not known. Increased knowledge about whether a distal radius fracture is a result of osteoporosis or an unfortunate fall is important for further clinical practice.

1.1 Low-energy distal radius fracture

A low-energy fracture is defined as a fracture that occurs with the trauma equivalent to that generated by a fall from standing height or lower[12]. It may also synonymously be called osteoporotic fracture or fragility fracture. In patients with osteoporosis, practically all types of fractures are more frequent. However, there are three kinds which are usually referred to as typical osteoporotic fractures, i.e. distal radius fractures, hip fractures and vertebral fractures[6].

1.1.1 Definition of distal radius fracture

Distal radius fracture was first mentioned by Petit in 1705[13] and further described by Pouteau in 1783[14, 15]. The first published paper on distal radius fractures was by Colles in 1814[16]. Colles described the type of distal radius fracture characterised by dorsal angulations of the distal fragment occurring within 2-3 cm of the distal end of the radius (Figure 1.1). A fall on the outstretched hand is the most common mechanism of injury. Other types of injury may cause different angulations and dislocations of the distal radius[17]. The majority of the distal radius fractures in the elderly are closed fractures where the overlying skin is intact. There are several treatment choices for dealing with a distal radius fracture. These depend on factors such as the mechanism of the injury, soft tissue condition, fracture type, intra-articular component of the fracture, age of the patient and quality of the bone. If there is no or minimal dislocation, the fracture is normally stabilised by a plaster cast[18]. External fixation is often the treatment choice if the fracture is unstable, and dynamic fixation appears to be a better choice than static fixation in some types of distal radius fractures[19].

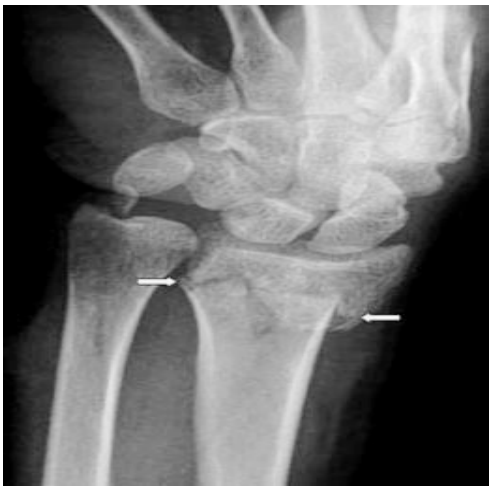

Figure 1.1 Fracture of the distal radius. From: American Academy of Orthopedic Surgeons, 2007.

1.1.2 Epidemiology of distal radius fracture

The total incidence of distal radius fractures in Norway is estimated to be 10.9 per 1000 women and 2.5 per 1000 men[20]. In a study from Bergen on adults over 20 years, the overall incidence of distal radius fractures was 3.8 per 1000, and 79% of the injured were women[21]. Most of the distal radius fractures in Bergen occur outdoors after a fall on slippery surfaces[21]. In older studies the incidence of distal radius fractures decreased or levelled off after the age of 60[21, 22]. However, in recent studies the incidence increases after the age of 45 years in women and continues to progress into older age[20, 23]. In younger age, the fracture is more common in boys than in girls, as confirmed by a study from Bergen on child fractures[24]. However, with increasing age, women predominate[3].

1.1.3 Consequenses of distal radius fracture

The long-term impact on quality of life after radius fracture is limited[25]. Most patients with a distal radius fracture have reduced function of the arm and pain during the first weeks after the fracture. Generally, distal radius fracture patients seem to attain arm and hand function about six months after the fracture, though many patients have residual symptoms associated with it[26, 27].

1.2 Osteoporosis

The clinical consequence of osteoporosis is the increased risk of fragility fractures[28, 29]. Osteoporosis is asymptomatic and may remain disregarded until a fracture occurs. It is a question of definition whether osteoporosis should be regarded as a condition or a disease.

1.2.1 Definition of osteoporosis

A descriptive definition of osteoporosis was formulated at a consensus development conference in Copenhagen in 1990: "Osteoporosis is a systemic disorder characterised by low bone mass and micro-architectural deterioration of the bone with a consequent increase in bone fragility and susceptibility to fracture"[1]. Bone fragility was also emphasised in 1994 by the US National Institute of Health Consensus Development Conference on Osteoporosis Prevention: "Osteoporosis is a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture"[29]. Normal versus osteoporotic bone is shown in Figure 1.2. The World Health Organisation (WHO) operationalised the definition by establishing specific criteria for use in diagnostic practice[30, 31], as listed in Table 1.1.

Table 1.1 Diagnostic criteria for osteoporosis[30, 31].

Normal: Bone mineral density (BMD) or bone mineral content (BMC) that is no more than 1 standard deviation (SD) below the mean of young adults
Osteopenia (low BMD): BMD or BMC between 1 and 2.5 SD below the mean of young adults
Osteoporosis: BMD or BMC 2.5 SD or more below the mean of young adults
Severe osteoporosis: BMD or BMC 2.5 SD or more below the mean of young adults in the presence of one or more fragility fractures

The aim of defining osteoporosis according to these criteria was that these cut-off levels should reflect lifetime fracture risk among postmenopausal women from observational

studies. Consequently, the definitions could be used to estimate the prevalence of osteoporosis[32]. BMD values were standardised as T-score and Z-score, where T-score is defined as the SD units from the young adult mean, and Z-score as the SD from the mean of age- and sex-matched controls[31]. However, this classification depends on the young adult mean and the SD in the selected reference database. Further, reference data are supplied by the manufacturers of the various densitometries and vary according to the manufacturer. This leads to different T-score values even though the BMD data are the same. To account for this, official positions have been defined for reference data, measurement sites and the use of T- and Z-scores[33]. The latest recommendation suggests that the reference standard should be based on BMD measurement at the femoral neck with dual-energy X-ray absorptiometry (DXA). The recommended reference database is the US National Health and Nutrition Examination Survey (NHANES III) for femoral neck measurements in women aged 20-29 years. An equal cut-off value for femoral neck BMD that is used to define osteoporosis in women can be used for men[33]. Osteoporosis may be diagnosed in women and men aged 50 years and older if the T-score at femoral neck is −2.5 SD or less. However, multiple skeletal sites can be used; e.g. osteoporosis can be defined as a T-score ≤ −2.5 SD in one of the following measurement sites: femoral neck, total hip or lumbar spine. The diagnostic sensitivity may be increased, but the prognostic ability is not improved[34]. The Z-score should be used rather than the T-score to evaluate BMD in people younger than 50 years[33, 35].

Several studies confirm that each 1 SD decline in BMD is associated with a 2-3 fold increase in the age-adjusted risk of hip fracture[36-38]. Although BMD is a strong predictor of fracture, it is only a surrogate measure. Variation in the level of BMD accounts for 60-70% of the variation in bone strength[39]. Bone strength also depends on the structural characteristics of the skeleton such as size, shape, geometry, three-dimensional architecture, micro-damage, remodelling action, and substance properites[39-41]. However, the micro-architecture and the other structural variables are difficult to measure. Methods to measure BMD are more readily available and large population samples can be measured in a relatively short time[42].

Fracture risk is also influenced by clinical factors, independently of BMD. The WHO developed the Fracture Risk Assessment Tool (FRAX®) algorithm to calculate the 10-year risk of hip fractures and major osteoporotic fractures (clinical spine, forearm, hip, or shoulder)[43]. FRAX® is based on clinical risk factors in combination with BMD. FRAX® has

been developed with the aim to better identify people at high risk of fracture so that treatments can be more effectively targeted[44]. The difficulty arises in identifying individuals at high fracture risk as fractures also occur in people with T-scores > −2.0 SD[45-47]. Acknowledging that BMD is obviously not the only factor determining bone strength and accepting the limitations of the WHO definition of osteoporosis, attention to BMD in this thesis is justified because BMD is very closely related to bone strength and fracture risk. Throughout this dissertation the term osteoporosis is used synonymously with the WHO definition, unless otherwise is stated.

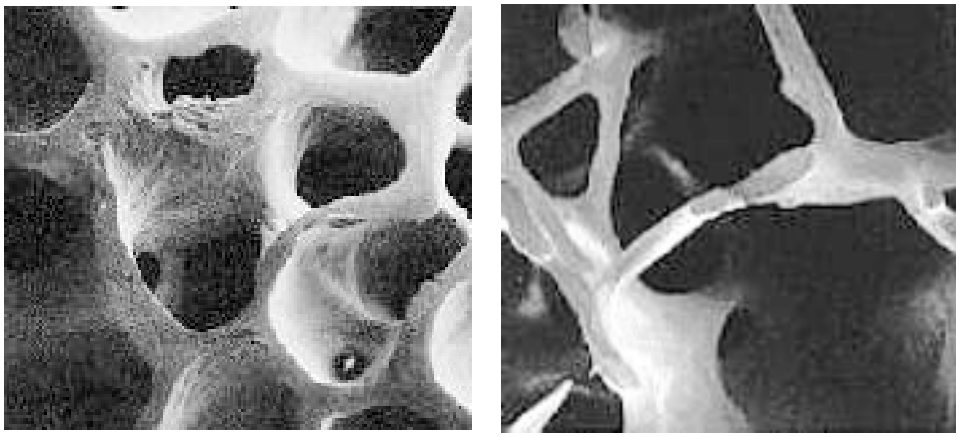

Figure 1.2 Normal and osteoporotic bone. From: Bone Health and Osteoporosis: A Report of the Surgeon General, 2004.

1.2.2 Epidemiology of osteoporosis

In Norway and the other Scandinavian countries the prevalence of osteoporosis and the incidence of low-energy fractures are among the highest worldwide[20-22, 48-51]. Approximately 250,000 Norwegian women and 50,000 men aged 50 years and older have osteoporosis[4]. Every year Norwegians suffer from about 9,000 hip fractures, 15,000 forearm fractures and 8,000 vertebral fractures[4]. In the year 2000 about 9 million new osteoporotic fractures occurred worldwide, of which 1.6 million were hip fractures, 1.7 million forearm fractures, and 1.4 million vertebral fractures[3].

1.2.3 Consequences of osteoporosis

Osteoporotic fractures cause pain, suffering and reduced quality of life for the patients and the societal economic consequences are high[3, 25]. Hip and vertebral fractures are related to

increased risk of mortality[52-56]. In a recently published long-term follow-up study from Australia all fragility fractures in older age was associated with increased risk of death[57]. Among women over 44 years, osteoporotic fractures cause more hospital days than any other disease[58]. In another study from Australia, roughly every second woman and one in four men aged 60 years will experience a fracture during their remaining lifetime[59].

1.3 Assessment of bone mineral density - Dual-energy X-ray absorptiometry

DXA is the most commonly used bone densitometry technique and is at present considered the "gold standard" for the non-invasive diagnosis of osteoporosis[42, 60]. Femoral neck is the recommended DXA site for estimating hip fracture risk[33]. Due to the two-dimensional scan used in DXA, only areal density, not true volumetric density is provided[61]. The BMD derived from DXA is the mass of bone mineral content (BMC) per unit area; not per unit volume. As BMD is not directly proportional to bone area, differences in bone thickness is not taken into account[62].

1.4 Bone metabolism

Bone consists of an organic extra-cellular matrix containing mineral deposits where the major portion is collagen which accounts for 90% of skeletal weight in the adult. The skeleton undergoes continuous remodelling during life. Multinucleated cells, osteoclasts, resorb the calcified matrix, whereas osteoblasts synthesise new bone matrix which undergoes subsequent calcification. The remodelling process maintains bone strength and calcium homeostasis. About 10% of the skeleton is renewed each year. During about two weeks the bone resorption phase takes place. The osteoid formation phase takes about three months whereas the subsequent mineralisation phase takes up to one year[63]. Under regular conditions, bone resorption and formation are coupled processes. During the growth spurt bone turnover increases: formation exceeds resorption resulting in a net bone gain. At older age (postmenopausal), resorption exceeds formation, resulting in net bone loss. Bone turnover is higher in trabecular bone than in cortical bone. Trabecular bone is common in the distal forearm, hip and spine. The resorbing cells are modulated by cytokines and hormones, e.g. parathyroid hormone (PTH), 1.25-dihydroxyvitamin D ($1.25(OH)_2D$), and calcitonin.

The formation of osteoclasts is regulated by inactive osteoblast cells which cover the bone surface. In osteoporosis the bone turnover is increased[64].

1.4.1 Calcium

Calcium plays an important role in the growth of the skeleton and in cell development. Calcium is also important in preventing osteoporosis and fractures[65]. In the circulating blood, calcium is bound to proteins (albumin). The degree of protein binding depends on the pH level of the blood. The degree of binding is high in alkalosis and low in acidosis; a high pH level gives a low calcium level in the blood. Optimal calcium intake to ensure bone homeostasis seems to be 500-800 mg daily[29]. Elderly people with decreased BMD or osteoporosis may benefit from a higher intake[66, 67]. However, some data on vascular events suggest that a high supplemental calcium intake might have an adverse effect on vascular health[68, 69].

1.4.2 Parathyroid hormone

PTH is a polypeptide hormone formed in the parathyroid glands. Synthesis and release of the hormone are regulated by the calcium concentration in the plasma. Low plasma calcium concentration leads to increased PTH release. PTH is essential in the calcium homeostasis by acting directly on bone (stimulating mineral resorption) and kidney (stimulating calcium reabsorption). PTH also stimulates 1-α-hydroxylase action and thus increases the production of $1.25(OH)_2D$, which increases the intestinal calcium absorption[70].

1.4.3 Vitamin D

The term vitamin D comprises the two fat-soluble components vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Vitamin D_3 is synthesised from 7-dehydrocholesterol in the skin during exposition to ultraviolet radiation, and this synthesising process is the most important vitamin D source in humans[71]. Vitamin D_3 is also the major type of nutritional vitamin D[72]. Vitamin D_2 comes mainly from vegetable sources, and vitamin D_3 comes from animal sources like fatty fish and cod liver oil[73] in addition to vitamin D enriched food like margarine and semi-skimmed milk[72]. In humans, vitamin D is hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D)[74]. The circulating level of 25(OH)D is the most reliable marker for vitamin D status[72]. Severe and moderate vitamin D deficiency are defined as s-

25(OH)D lower than 12.5 nmol/L and 12.5-25 nmol/L, respectively[71]. The most favourable level of vitamin D in respect to bone health has not been established but different thresholds have been proposed; s-25(OH)D > 30, > 50 and > 75 nmol/L[71, 75, 76]. However, results on the relationship between 25(OH)D, BMD, bone turnover, lower extremity function and falls, indicate that 50 nmol/L is an appropriate threshold to classify vitamin D inadequacy[77]. However, s-25(OH)D above 75 nmol/L is thought to be beneficial for the prevention of e.g. fractures, low BMD, high risk of falling, extremity weakness, poor dental health, cancer and hypertension[78, 79]. Nevertheless, the evidence for an association of 25(OH)D levels with fractures is not consistent[73].

One of the main functions of vitamin D is to contribute to maintaining stable serum calcium level. If serum calcium decreases, PTH is secreted from the parathyroidea. This stimulates the renal hydroxylation of 25(OH)D into $1.25(OH)_2D$ which in turn increases the intestinal calcium absorption, the renal calcium reabsorption and the bone remodelling[73]. Thus, vitamin D and PTH together regulate calcium metabolism and influence bone health in balance with the hormone calcitonin that prevents hypercalcemia by stimulation deposition of calcium in the skeleton[65].

Epidemiology of vitamin D deficiency

Worldwide, it is estimated that 1 billion people have vitamin D deficiency or insufficiency[80]. In Norway, a high prevalence of vitamin D deficiency among immigrants has been found. For example, in the study by Meyer et al[81], mean 25(OH)D was 75 nmol/L in Norwegian women and 25 nmol/L in Pakistanis living in Norway. The high prevalence of vitamin D deficiency in immigrant groups is also mentioned in other studies[82-85]. In fracture patients from Germany and Northern Ireland it has been demonstrated that a large proportion of those with a distal radius fracture have vitamin D inadequacy[86, 87].

Consequences of vitamin D deficiency

Severe deficiency of vitamin D is related to impaired mineralisation of recently produced bone and leads to rickets in children and osteomalacia in adults[72, 88, 89]. Low vitamin D levels are known to be associated with impaired general health and there is evidence of a link with several common diseases[90] as well as increased mortality[91, 92]. In less severe vitamin D deficiency, the decreased gastrointestinal absorption and renal reabsorption of calcium

stimulates the production of PTH, leading to secondary hyperparathyroidism and thereby to calcium release from the skeleton. Thus, people suffering from vitamin D deficiency are susceptible to osteoporosis and fractures[71, 93]. Vitamin D deficiency has also been associated with muscle weakness, leading to an increased risk of falling[94]. Vitamin D has a direct effect on muscle strength modulated by specific vitamin D receptors present in human muscle tissue[95].

1.5 Risk factors for osteoporotic fractures

Lifetime fracture risk is associated with a number of factors[96]. These are factors related to the trauma and/or factors related to bone strength[97].

1.5.1 Falls

Most low-energy fractures occur in connection with a fall, and a previous fall is a strong predictor for new falls[98-100]. The prevalence of falls is higher in women than in men[21, 101]. A number of factors determine whether a fall results in a fracture or not. These mechanisms can be classified as internal and external factors. Internal factors are bone strength, the person's height and weight, orientation of the fall, width of the movable tissue covering skeletal structures, nutritional status, inactivity (lack of exercise), medical condition, medications, and alterations related to aging (reduced visual acuity and cognitive impairment). External factors include the energy involved when falling, slippery surfaces such as ice or snow, resistance of the surface, light settings and grips[99, 102].

1.5.2 Bone mineral density

BMD increases during adolescence and peaks at the age of 25-30 years, plateaus to the age of 40, and declines after that[28]. Thus, attaining a high peak bone mass may protect against osteoporosis in later life. The prevalence of low BMD and osteoporosis increases radically with age; in women aged 50-59 years the worldwide prevalence is about 4%, while the prevalence is 40% in women aged 80 years and older[103]. Many studies show that next to age and sex, BMD is the strongest predictor of osteoporotic fractures[36, 38, 104, 105], and that BMD of the proximal femur site is the best predictor of hip fracture[37, 106]. The association between BMD and fracture risk is continuous, with more than a doubling of fracture risk for each SD decline in BMD[106].

1.5.3 Age, gender and ethnicity

The risk of osteoporotic fractures increases with age[23, 107] and is generally higher in women than men[23, 101]. About three of four hip fractures occur in women[101]. Generally, bone diameter and cortical thickness are greater in men than women. The risk/occurrence of distal radius fractures increases after the age of 45 in women[20, 23], while few hip fractures occur before the age of 50[101]. Data from Sweden showed that lifetime risk for distal radius fracture at age 45 was 22% in women and 5% in men[23].

The incidence of hip fractures is higher in women of Caucasian origin than in women of Asian or African origin[97]. This has been demonstrated by comparing fracture incidence between countries, but also between different ethnic populations within the US[108].

1.5.4 Genetics

Heritability data show that genetic factors may explain up to 80% of the difference in BMD[109]. A family history of hip and/or distal radius fracture is a risk factor for distal radius fracture[110]. However, a meta-analysis showed that a parental history of fracture gave an increased risk of fracture independently of BMD[111]. Certain genes have been identified to be associated with variations in BMD[112, 113] and the risk of fractures[109, 114].

1.5.5 Previous fracture

A history of a prior fracture at any location is a significant risk factor for subsequent fractures[100, 115]. One of the strongest risk factors for distal radius fractures is a previous low-energy fracture[116-118]. Women with a prior distal radius fracture have a threefold risk of a new distal radius fracture[115], and a distal radius fracture is a risk factor for a subsequent hip fracture both in women and men[119]. Any previous fracture is associated with a twofold relative risk of any subsequent fracture[115, 120].

1.5.6 Body weight and body height

Low body mass index (BMI) or low body weight is strongly associated with low BMD[121, 122] and increased fracture risk in both genders[123-125]. High BMI seems to protect against distal radius fracture[117, 126]. Weight loss is also related to a reduction in BMD and an increased risk of hip fracture in women and men[127-130], whereas weight gain is found to decrease the risk of hip fracture[131]. Body height is positively associated with the risk of hip fractures[125, 131].

1.5.7 Physical inactivity

It has been documented that weight-bearing activities increase BMD[132], and that physical activity protects against hip fracture[133, 134]. A recent review of prospective cohort studies concluded that moderate to vigorous physical activity was associated with a reduction of hip fractures of about 38% in women and 45% in men[135]. However, results from studies investigating physical activity and fracture risk are inconsistent[117, 136]. The duration and intensity of the training protocol may affect the results. Weight-bearing activities such as walking, running or strength training are beneficial in strengthening bones[132, 137]. Muscle strength is improved by strength training, which may reduce the tendency to fall, thus reducing the risk of fractures[138]. Both inactive and very active people have a higher tendency to fall than people with moderate activity[135].

1.5.8 Nutrition

Insufficiencies of specific nutrients have been shown to affect bone[139]. Calcium, vitamin D, vitamin B_{12} and folate are frequently under-consumed by older people, and a relationship between poor diet and mortality is well recognised[139]. In a study from Oslo, participants with a vitamin D intake of less than 2,5 µg per day had an increased risk of hip fractures[140]. Randomised controlled trials show that high doses of vitamin D (700-1,000 IU per day, i.e. 17.5-25 µg) reduce both the risk of falling[141] and the risk of hip and other non-vertebral fractures[142]. In addition, other nutrients have been proposed as being important, including vitamin A[143], vitamin K[144], protein[145] and fat[146], including omega-3 fatty acids. However, vitamin A seems to have a negative effect on bone health. For example, in some studies a high dietary vitamin A intake was associated with a higher fracture risk in the general population, and with increased risk of hip fractures[147, 148], and low BMD in women[148]. In a Norwegian study, women who reported having taken cod liver oil during childhood had lower forearm BMD than those who reported no such use[143]. In Norway, the vitamin A content of cod liver oil was recently reduced by 75%. However, in other studies no association between vitamin A, low BMD or fracture risk was found[149, 150].

1.5.9 Smoking

In both women and men current cigarette smoking is found to be associated with fractures in general[151], hip fracture[151, 152], and spine fracture, but not with distal radius fracture[152]. Furthermore, smokers have lower BMD and greater bone loss than non-smokers[153, 154]. The effect of smoking on fracture risk seems to be dose-dependent with an increasing risk with the years of smoking[152, 155]. Cigarette smokers have significantly lower body weight than non-smokers; however, lower BMI is unlikely to explain the increased risk of osteoporotic fractures in smokers[151].

1.5.10 Alcohol consumption

In some studies alcoholism is found to be a risk factor for any osteoporotic fracture, hip fracture[156, 157], and low BMD[158]. Increased fracture risk in alcoholics may result from the effect of ethanol or non-ethanol ingredients of alcoholic beverages on bone remodelling[159], nutritional deficiencies or co-morbidity which increases the risk of falling[156, 160]. The effect of alcohol on bone seems to be dose-dependent, and moderate alcohol consumption (2 units or less daily) is not related to osteoporotic fracture or low BMD[156]. Some data suggest a positive effect on bone health of a moderate alcohol intake[156, 161, 162].

1.5.11 Co-morbidities and medication

Many diseases, conditions, and medications are associated with increased risk of osteoporosis and fractures. Some types of medicine might increase fracture risk by increasing bone loss or having side effects which increase the tendency to fall. Fracture risk may be increased by diseases such as type I diabetes mellitus, primary hyperparathyroidism, hyper- and hypothyroidism, rheumatoid arthritis, stroke, hypertension, inflammatory bowel disease, celiac disease, gastrectomy, asthma, chronic obstructive pulmonary disease, cystic fibrosis, renal disease, anorexia nervosa, pernicious anaemia, Parkinson's, dementia, and psychiatric disorders[107, 131, 163-174]. Reasons for an association might be e.g. inflammation, malabsorption, malnutrition, or a higher fall rate.

1.6 Treatment guidelines for osteoporosis

Guidelines from NMA suggest medical treatment for osteoporosis after a low-energy fracture when the T-score is less than −2.0 SD in subjects aged 50 years and older[11]. Scotland and

Sweden have similar guidelines[175, 176], whereas other guidelines recommend treatment after low-energy fracture and a T-score ≤ −2.5 SD[177, 178]. On the other hand, the UK National Institute of Health and Clinical Excellence (NICE) guideline recommends treatment for all women aged 75 years and older who have experienced a low-energy fracture regardless of the results of BMD measurements[179]. The various guidelines are based on risk reduction of pharmacological treatment and cost-effectiveness studies[180-182] and on the fact that risk reduction is strongest in patients with low BMD and a previous fracture[183-186].

2. Aims of the study

A distal radius fracture results from a low-energy trauma exerted on a skeleton with varying degree of reduced bone strength and such a fracture may be the first sign of osteoporosis in women and men over 50 years old. Different guidelines exist as to which fracture patients should be treated for osteoporosis. However, previous studies of the prevalence of osteoporosis in distal radius fracture patients are relatively few and the number of participants is low[187-192], and only some of the studies on this topic have included a control group[188, 192, 193]. Neither the proportion of fracture patients in need of osteoporotic treatment according to Norwegian guidelines nor the risk of future hip fracture in a radius fracture cohort are known at present. Furthermore, investigations of vitamin D status in distal radius fracture patients and matched controls have as far as we know not previously been published. In Norway, none of these questions have hitherto been addressed.

Thus, the overall aims were to investigate firstly the prevalence of osteoporosis in distal radius patients, secondly the association between distal radius fractures and osteoporosis, and thirdly the association between distal radius fractures and vitamin D inadequacy.

The specific aims were to:
1) Examine whether distal radius fracture patients have lower BMD than expected with regard to age and gender, and to estimate the risk of hip fracture and any osteoporotic fracture in this group of patients.

2) Compare the prevalence of osteopenia and osteoporosis between individuals with low-energy distal radius fracture and sex- and age-matched controls, and examine whether the observed differences in BMD between patients and controls could be explained by clinical risk factors.

3) Determine vitamin D status (s-25(OH)D) in female and male low-energy distal radius fracture patients compared with matched controls, and investigate whether observed differences in vitamin D between patients and controls could explain the differences in BMD.

3. Participants and methods

In 2003 an automatic referral to bone densitometry was etablished for all patients aged 50 years and older who suffered a low-energy distal radius fracture in the three Norwegian towns Bergen, Kristiansand, and Skien. This practice was based on the Fracture Liaison Model set up in Glasgow[191, 194].

3.1 Study design and population

The distal radius fracture patients were successively recruited from the referral centers for orthopedic trauma at the Bergen Accident and Emergency Department (AED) and Haukeland University Hospital (HUH) in Bergen (Papers I, II and III), Sørlandet Hospital in Kristiansand (Paper I) and Telemark Hospital in Skien (Paper I). The patients in Bergen were recruited from October 2003 to October 2007, in Kristiansand from December 2003 to December 2007 and in Skien from March 2003 to November 2007. The patients and controls were invited to the osteoporosis clinics for measurement of BMD, clinical risk score based on a questionnaire, and blood samples.

A total of 2,349 women and 357 men were treated for a low-energy distal radius fracture in the catchment areas during the recruitment period and were invited to participate (Paper I). Of these, 67% of the women (n=1,576) and 61% of the men (n=218) came for examination. figure 3.1 gives an overview of the study population.

In Papers II and III the subgroup of distal radius fracture patients from Bergen AED and HUH were included and a matched control group recruited in the period from April 2008 to June 2009 were included. During the inclusion period 1,252 female and 185 male patients were treated for low-energy distal radius fractures at Bergen AED and HUH. The study sample in Paper II comprised 664 female and 85 male patients aged 50-90 years. The corresponding numbers for Paper III were 575 and 72, respectively (Figure 3.1). The reasons why some patients did not participate and why some were excluded are described in Table 3.1.

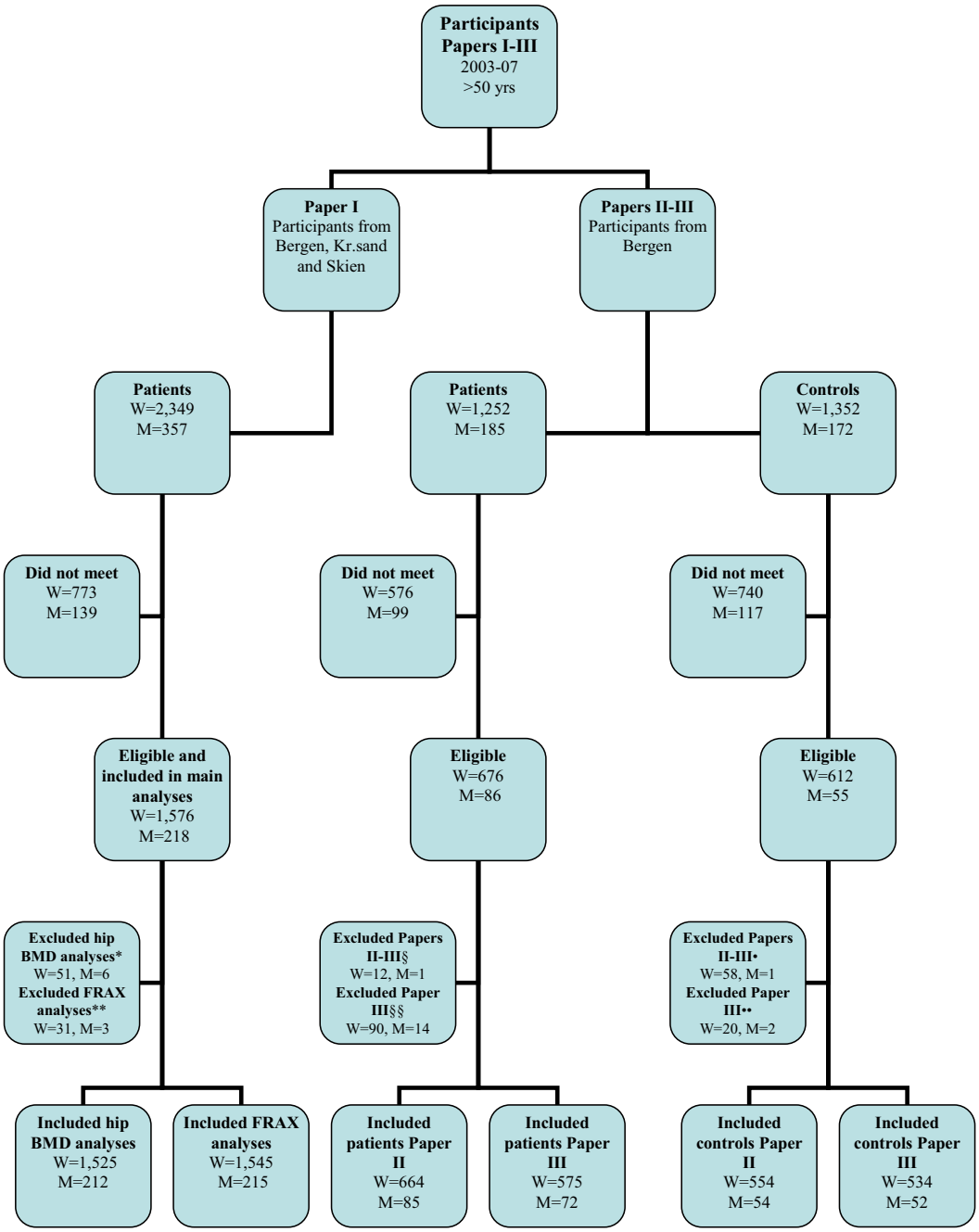

Figure 3.1 Flow-chart of the distal radius fracture patients and controls.

W: women, M: men.*No hip BMD scans: W=51, M=6, **Participants >90 yrs: W=25, M=3, non-Caucasian: W=6. §Participants >90 yrs: W=5, >6 months from fracture to BMD scan: W=7, M=1. §§No blood samples: W=89, M=13. •Previous low-energy distal radius fracture: W=54, M=1. No BMD scans: W=4. ••No blood samples: W=20, M=2.

Table 3.1 An overview of why some patients did not participate and why some were excluded in Papers II and III.

	Female patients	Male patients
Did not meet for unknown reasons	230	61
Dementia, confusion or illness	194	27
Previous evaluation for osteoporosis	117	4
Tourists	35	7
Evaluated more than 6 months after the current fracture	7	1
Older than 90 years	5	0
No blood samples*	89	13
Total	677	113

*Relevant for Paper III.

Control subjects were recruited from the general population in the same area as the fracture patients. They were randomly selected by Statistics Norway from the Norwegian Population Registry, matched by town of residence, age ($\pm$ 2 years), sex, and month of examination. Two control subjects per case were selected and invited by mail to participate; 1352 women and 172 men. The study sample in Paper II comprised 554 female and 54 male controls aged 50-90 years. The corresponding numbers for Paper III were 534 and 52 (Figure 3.1).

3.2 Demographic and clinical data

3.2.1 Questionnaires

The same self-administered questionnaire was used for all distal radius fracture patients (Appendix 3) and a similar questionnaire was used for the controls (Appendix 4). The questionnaire was handed out and filled in on the day of examination and participants were offered help by an experienced nurse if needed.

3.2.2 Bone mineral density measurements

All scanning procedures and analyses were conducted by trained medical staff following the same protocol. BMD was measured by DXA at all study sites. Prodigy (GE Lunar, Madison, Wisconsin) was used in Bergen and Kristiansand and EXPERT-XL (GE Lunar, Madison, Wisconsin) was used in Skien. The same DXA equipment was used during the whole study period. The results were based on the measurements at total hip, femoral neck, and L2-L4. The measurement regions of the hip are shown in figure 3.2.

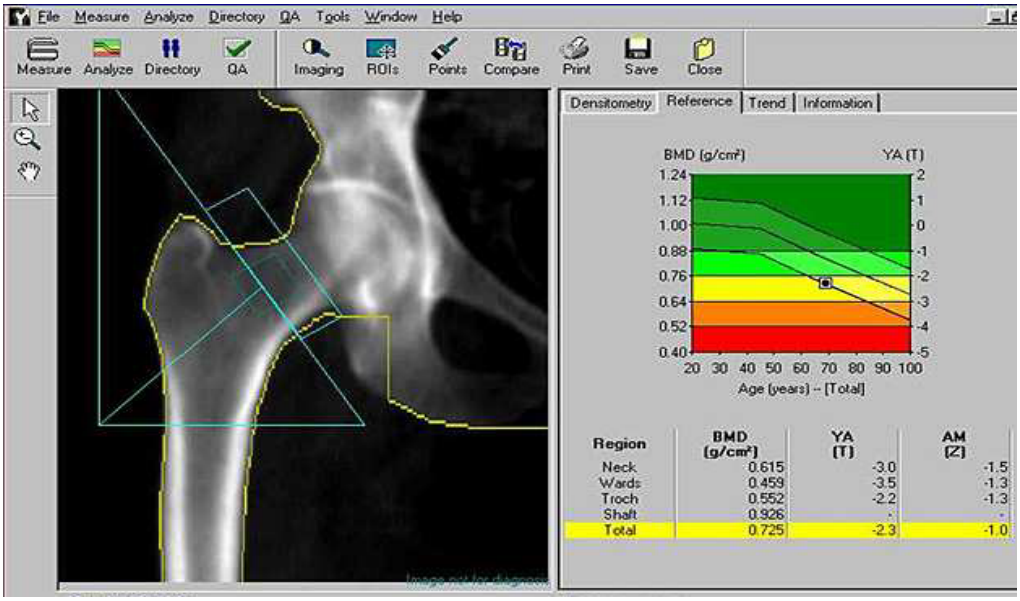

Figure 3.2 Proximal femur DXA scan showing the measurement regions; femoral neck (oblong box), Ward's area (box), trochanter (upper triangle), shaft (lower triangle), and total hip.

The DXA machines were calibrated daily and were stable during the whole examination period. The *in vivo* short-term precision for total hip, femoral neck and L2-L4 measurements was 0.77%, 1.47%, and 1.36% in Bergen, 0.89%, 1.56%, and 1.19% in Kristiansand, and 0.80%, 1.58%, and 1.50% in Skien, respectively. The *in vitro* long-term precision expressed as the coefficient of variation (CV %) was 0.86% in Bergen, 0.62% in Kristiansand, and 0.92% in Skien, respectively. A European spine phantom (ESP) was used to compare the three DXA machines, and no significant differences were found.

The average time from current fracture to BMD assessment and data collection at the osteoporosis clinics is shown in Table 3.2. In Papers II and III, eight patients examined more than 6 months after the fracture were excluded.

Table 3.2 Time in days from the current distal radius fracture to data collection. Mean number of days and range.

	Paper I	Paper II	Paper III
Female patients	49 (0-634)	66 (6-169)	63 (7-169)
Male patients	41 (0-183)	63 (18-156)	58 (18-152)

BMD was categorised according to the definitions of osteoporosis (T-score ≤ –2.5 SD), osteopenia (T-score < –1.0, > –2.5 SD), and normal BMD (T-score ≥ –1.0 SD)[31]. In addition, the NMA treatment guidelines (T-score ≤ –2.0 SD)[11] and a Z-score cut-off < –1.0 SD were used in Paper I.

3.2.3 Reference population

BMD T-score and Z-score were calculated from a combined European/US reference population as incorporated in the accompanying software[195, 196]. Scores were gender-specific and the reference population for the calculation of T-score was young adults aged 20-40. A Z-score < –1.0 SD was defined as reduced BMD (>1 SD below the age- and weight-matched mean of Lunar).

3.2.4 Fracture risk assessed by FRAX®

As no FRAX® model is accessible in Norway, we used the Swedish FRAX® model, version 3.0, to estimate the 10-year risk of hip fractures and any major osteoporotic fractures (clinical spine, forearm, hip, or shoulder) (Paper I)[43]. The algorithm is based on a series of meta-analyses of data from 12 studies from around the world, including North America, Europe, Asia and Australia. It has been validated in independent cohorts[104]. The risk factors included in the model are: age, sex, weight, height, femoral neck BMD (g/cm^2), previous fracture, parental history of hip fracture, current smoking, use of oral glucocorticoids for more than three months, rheumatoid arthritis, other secondary causes of osteoporosis (type I diabetes, osteogenesis imperfecta, hyperthyroidism, hypogonadism, early menopause (< 45 years), chronic malnutrition, malabsorption and chronic liver disease), and alcohol intake of three or more units per day. The model can be used with or without femoral neck BMD[43]. The FRAX® calculations in our study were performed by the WHO collaborating centre for metabolic bone diseases.

3.2.5 Biochemical analyses

All serum samples were analysed at the Hormone Laboratory, HUH and the Laboratory for Clinical Biochemistry, HUH (Paper III). A radioimmunoassay from Immunodiagnostic System, Boldon, UK was used to measure 25(OH)D. The interassay CV percentages were 8.2%, 8.1%, and 7.3% for concentrations of 19.6, 56.7, and 136 nmol/L, respectively.

Colorimetric assays with a Roche/Hitachi Modular analyser (Roche Diagnostics GmbH, Germany) were used to measure serum calcium and albumin. The interassay variations were 2.0% for calcium at a concentration of 2.44 mmol/L and 2.0% for albumin at a concentration of 44.0 g/L. Serum calcium was corrected for serum albumin by the equation: serum calcium (mmol/L) + (40 – serum albumin) x 0.02.

3.3 Statistical analyses

Paper I

The proportion of patients with indication for treatment (T-score ≤ −2.0 SD) and osteoporosis (T-score ≤ −2.5 SD) were estimated among women and men and in ten-year age spans. BMD levels in our group of fracture patients were compared with the reference population in the Lunar database, and the proportion of individuals with a Z-score ≤ −1.0 SD was evaluated[195]. Assuming a normal distribution, the expected proportion of Z-score ≤ −1.0 SD is 16% by default. The 95% confidence interval (CI) range for proportions of patients having a Z-score of ≤ −1.0 SD was calculated using the equation for binomial distribution[197].

Paper II

Independent sample t-tests were used for comparison of continuous variables and chi-square tests for comparison of categorical variables between fracture patients and controls and between age categories. Age was stratified at 50-64 and 65-90 years. Women were further divided into ten-year age spans. Odds ratios (ORs) for distal radius fracture were estimated in unadjusted conditional logistic regression analyses separately for the different demographic and clinical risk factors. Variables from the unadjusted analyses with a p-value ≤ 0.20 were included in the adjusted analyses.

Paper III

Independent sample t-tests for comparison of continuous variables and chi-square tests for comparison of categorical variables between fracture patients and controls were used. ORs for distal radius fracture were estimated in unadjusted and adjusted conditional logistic regression analyses for 25(OH)D. In the adjusted analyses the estimates of s-25(OH)D were adjusted for femoral neck BMD (g/cm^2), BMI (kg/m^2), and smoking. A generalised additive logistic regression model (GAM) was used for the dose-response relation between 25(OH)D

nmol/L, and OR for distal radius fractures. The model was adjusted for femoral neck BMD (g/cm^2), BMI (kg/m^2), age, and smoking.

P-values below 0.05 were considered statistically significant. All analyses were performed using SPSS software for Windows, version 15.0 (SPSS Inc., Chicago, Illinois).

3.4 Approvals

The study was approved by the Norwegian National Data Inspectorate and the Regional Committee for Medical Research Ethics, Western Norway. All participants gave written consent to participate.

4. Main results

The main results from the three papers (I, II and III) are presented below, together with some additional results for the study presented in Paper II.

4.1 Paper I

The prevalence of distal radius fracture patients with indication for treatment according to NMA guidelines (T-score ≤ −2.0 SD) at femoral neck was 51% among women (n=1,525), and 38% among men (n=212). The prevalence of osteoporosis (T-score ≤ −2.5 SD) was 31% in women and 20% in men. About 64% of the women and 49% of the men had a T-score ≤ −2.0 SD at one or more measurement sites. Corresponding figures for osteoporosis were 45% and 33%, respectively. Within ten-year age groups the prevalence of a T-score ≤ −2.0 SD was approximately equal in women and men. The proportion of women and men aged 75 years and older with osteoporosis was 54% and 33%, respectively. Compared to the reference population, a reduced age and weight adjusted BMD (expressed as Z-score) in the fracture group was observed. In fracture risk assessment analyses by FRAX® the ten-year risk of hip fracture calculated with BMD was 9% in women and 6% in men. The corresponding percentages for women and men with osteoporosis were 18% and 16%. 18% of the women with a FRAX® score >15% for the risk of hip fracture calculated with BMD did not have osteoporosis. The corresponding figure in men was 15%. When the same figures were calculated without BMD, 46% of the women and 44% of the men did not have osteoporosis.

4.2 Paper II

The prevalence of osteoporosis measured at femoral neck was 34% in female patients (n=654) and 10% in female controls (n=546). Corresponding values in male patients (n=85) and controls (n=54) were 17% and 13%, respectively. When all three measurement sites were considered, the prevalence increased in both patients and controls (Table 4.1). In the age group 50-59 years, 18% of the female patients and 5% of the female controls had osteoporosis. The corresponding numbers for the age group 60-69 years were 25% and 7%. Among men aged 50-64, 14% of patients and 11% of controls had osteoporosis. The corresponding figures for the age group 65-90 years were 20% and 15%. In conditional

logistic regression analyses adjusted for BMI, hip fracture in a parent, previous fracture, and early menopause, osteopenia (OR=2.7, 95% CI: 1.9-3.9, p<0.001), and osteoporosis (OR 6.8, 95% CI: 4.1-11.2, p<0.001) were significantly associated with distal radius fractures in women. Osteoporosis (OR=8.1, 95% CI: 1.4-47.4, p=0.021) was significantly associated with distal radius fractures in men after adjustment for BMI, current smoking, and hip fracture in one of the parents.

Table 4.1 Prevalence of normal BMD, osteopenia and osteoporosis in one of the measurement sites total hip, femoral neck or spine (L2-L4). Data are given as numbers (%).

	Female			Male		
	Patients	Controls	p-value*	Patients	Controls	p-value*
Normal BMD	63 (10)	150 (27)	< 0.001	11 (13)	15 (28)	0.063
Osteopenia	273 (41)	276 (50)		45 (53)	27 (50)	
Osteoporosis	328 (49)	128 (23)		29 (34)	12 (22)	

*Overall p-value for the categorised variable. Normal BMD: T-score ≥ –1.0 SD. Osteopenia: T-score < –1.0, > –2.5 SD. Osteoporosis: T-score ≤ –2.5 SD.

4.3 Paper III

Mean s-25(OH)D was 66.5 nmol/L in female patients (n=575) compared to 78.7 nmol/L in female controls (n=534) (p<0.001). The corresponding figures in male patients (n=72) and controls (n=52) were 64.5 and 77.0 nmol/L (p=0.017), respectively. In conditional logistic regression analyses adjusted for BMI (kg/m^2), smoking, and BMD (g/cm^2), s-25(OH)D < 50 nmol/L (OR=2.3, 95% CI: 1.5-3.6, p<0.001), and 50-75 nmol/L (OR=1.7, 95% CI: 1.2-2.5, p=0.005) were associated with distal radius fractures in women, and s-25(OH)D < 50 nmol/L (OR=6.27, 95% CI: 1.2-33.7, p=0.032) was associated with distal radius fractures in men. A dose-response relationship between vitamin D and distal radius fracture was found for vitamin D levels up to approximately 100 nmol/L in both genders.

5. Discussion

The strengths of this study are that we were able to include a large number of patients with distal radius fractures consecutively in the clinical work, and a large number of matched controls.

5.1 Methodological considerations

This study is an epidemiological research project. A major goal for epidemiological research is to identify subgroups in populations that are at high risk of disease.

5.1.1 Study design

Paper I is a cross-sectional study (descriptive study); this study design is useful for estimating prevalence. A cross-sectional study can also be suggestive of potential risk factors when an association is found. We have used this design to estimate the prevalence of osteoporosis among patients with a distal radius fracture. Compared to the reference population, a reduced BMD was observed. Low BMD is a risk factor for fracture. Generally, a cross-sectional study design has limitations in establishing a temporal relationship between exposure and outcome. However, it seems unlikely for a fracture to occur first and osteoporosis second because it takes several years to develop osteoporosis.

Papers II and III are case-control studies; these are classified as analytic studies because they make use of a comparison group. In these two papers, the outcome variable is radius fracture. Case-control studies are frequently used in epidemiological research and allow researchers to evaluate both diseases with long latency periods and exposure variables associated with a given outcome. The outcome is always identified previously to the exposure, thus case-control studies are retrospective in character[198].

5.1.2 Selection bias

Participation rate

In spite of the large number of patients and controls, selection bias may have influenced our results because of a large proportion of non-attendees among both cases and controls. The

oldest age groups had a particularly low participation rate. Demographic comparisons between attendees and non-attendees are not fully available, but we have information about why some patients from Bergen did not participate. Many female patients had previously been examined for osteoporosis and therefore chose not to participate. If many of them already had been diagnosed with osteoporosis, the prevalence of osteoporosis in our study may have been underestimated, leading in turn to a possible underestimation of the difference in BMD between patients and controls. Drop-out reasons among controls are unknown, but some control subjects may also have declined to participate because they had already been treated for osteoporosis. If this were the case, the prevalence of osteoporosis may have been underestimated in this group as well. Thus, selection bias might have affected both groups. The degree of possible underestimation of osteoporosis and its influence on the results are unknown.

5.1.3 Information bias

BMD measurements

The operator technique may influence BMD outcome (Paper I) and exposure (Papers II and III). In this study the procedures recommended by the manufacturer of the bone densitometry machines were strictly adhered to and the scans revealed no major errors (Papers I, II and III). The same stable DXA device was used throughout the inclusion period at each study centre. We tested the reliability of the bone densitometry scans at the study sites with the European Spine Phantom (ESP), and found no significant differences between the results at the different study sites.

Timing: In the present study, DXA measurements and assessment of clinical risk factors were conducted on average within two months of the current distal radius fracture. The maximum delay from fracture to examination was 634 days (Table 3.2). In Papers II and III we decided to exclude patients with DXA measurements and blood samples taken more than six months after the current distal radius fracture. This was done to avoid results being affected by e.g. the use of anti-osteoporotic treatment between fracture and examination. Thus, theoretically the BMD results in Paper I could have been biased by delayed examination. However, only one man and seven women had their BMD measured after 6 months. No differences were observed in results after excluding these participants. BMD was measured by DXA at the total hip, femoral neck and spine (L2-L4), and not at the

wrist. These measurement sites were chosen because data have shown that BMD measurements at these sites are better predictors of e.g. hip fracture risk[38] than measurements from peripheral sites[33, 35]. However, measurement at the wrist is a better predictor for fracture risk at the distal radius[35].

Reference population: BMD was measured as T-score and Z-score derived from a combined European/US reference population in the accompanying software[195, 196]. As we did not have any young healthy reference group from our own districts, this reference population was used as a control group in our study (Paper I). Ideally our data should have been compared with a large reference group from the districts of Bergen, Kristiansand, and Skien. The Lunar reference population used has been found to correspond well with the general Norwegian population at all age groups[195, 199]. However, in a study from Tromsø, the authors found that the prevalence of osteoporosis at the femoral neck was 20% in women and 14% in men aged 70 years and older, using the Lunar reference material for T-score calculations. The prevalence increased significantly to 35% in women and 19% in men when T-scores were calculated on the basis of the young adult mean BMD (age group 30-39 years) in the study population[200]. Thus, a population-specific T-score estimation may have led to a higher proportion of osteoporosis among both patients and controls in our study. According to the International Society for Clinical Densitometry (ISCD), international reference data are recommended for diagnostic purposes as we have done. The comparison made in Paper I by evaluating Z-scores is, however, highly dependent on the suitability of the reference population. The generally lower BMD among Norwegians will overestimate the importance of BMD for distal radius fractures. In Paper II we have included a specific control population to account for this possible bias.

Assessment of distal radius fractures

All distal radius fractures among the patients were radiographically confirmed. There is some difficulty in the classification of fractures as low-energy or high-energy. The fall mechanism can vary, and a fall can in fact resemble a high-energy trauma even if it happens from standing height.

Questionnaires

The questionnaires were derived from similar questionnaires, such as the Hordaland Health Study, and based on known risk factors for osteoporosis from previous research. Differences in interpretation of the questionnaire could have resulted in an information bias.

Previous fractures: Among the patients and controls, previous distal radius fractures after the age of 50 years were self-reported. The controls who reported a previous distal radius fracture were excluded from the study. The retrospective study design may introduce recall bias, and the controls may have had difficulty in knowing what kind of fractures we were asking for. Thus, earlier distal radius fracture patients might have been misclassified as controls. Furthermore, self-reported fractures have low validity[201]. Other types of fractures were also self-reported, which could have underestimated or overestimated the proportion of previous fractures.

FRAX®: The optimal estimate of alcohol consumption as a risk factor according to FRAX® is three or more units per day. This is a yes/no question in the FRAX® algorithm. In our study, participants only reported whether or not they considered themselves to be alcohol abusers. If moderate alcohol consumption is a risk factor for fractures, our results may have been biased and the 10-year risk of fractures underestimated. As an example, in a woman aged 60 years, with BMI 23 kg/m^2, a low-energy fracture and normal BMD, the hip fracture risk increases by 0.7% when alcohol of three or more units per day is reported. Similarly a woman with osteoporosis who reports three or more units of alcohol per day increases her FRAX® risk by 3%.

Patients and controls

The Norwegian population suffers more fragility fractures than other populations[4, 48, 202, 203], and within Norway, regional differences in hip BMD have been documented, e.g. lower hip BMD among women and men aged 60 years and above from Bergen compared to Tromsø[204]. We therefore found it important to include a matched control group from the same geographical area as the distal radius fracture patients. All participants in our study were examined at the same clinic, by the same staff, in the same month of the year as their matched fracture patients, with the same DXA machine, and the with same assay for 25(OH)D, which was stable throughout the inclusion period. However, a weakness of our

study is that our control subjects were included from six months to four years after the patients were assessed. It would have been a more reliable design if we had included the controls at the same time as the patients.

Biochemical analyses

The association between vitamin D and fracture is based on the assumption that the vitamin D level we have measured reflects the normal vitamin D level of the individual (Paper III). Our vitamin D results might have been influenced by time spent abroad in sunnier countries, or the use of a solarium previously to the blood tests. Unfortunately, we did not ask for this information. High levels of sun exposure in a low proportion of participants may have led to a small overestimate of vitamin D in both groups. Blood samples were handled similarly regardless of group. Equivalent procedures were performed for all participants and the blood samples were prepared for analysis according to strict procedures. So although the controls were included after the patients, we believe the validity of the vitamin D blood samples was satisfactory as the CVs were 8.2%, 8.1%, and 7.3% for concentrations of 19.6, 56.7, and 136 nmol/L, respectively.

5.1.4 Confounding

Paper II

The controls were matched at inclusion and as we used conditional logistic regression analyses, which are designed for matched case-control studies, adjustment for age was not needed as this was a matching variable. In this kind of analysis, a missing variable leads to exclusion of the matched pair. For example, if the variable previous fracture is lacking in a fracture patient, the matched control (the pair) is excluded from the analysis. ORs for distal radius fracture were estimated in unadjusted and adjusted regression analyses independently for the different demographic and clinical risk factors. We have included potential confounding variables in the analyses previously reported in the literature. We can however not rule out that some data may have been insufficiently measured or controlled for, and there may be residual confounding. Misclassification of information regarding hip fracture in a parent, previous fracture, and early menopause may have occurred, but the extent and impact of such bias are probably minor. Further, we decided to use the categorical BMI (< 22 kg/m^2) variable in the regression analyses. The continuous variable, BMI kg/m^2, was tested but the results did not change significantly compared to the findings when using the

dichotomized variable. Age (± 2 years) was one of the variables we used in matching the controls, and advanced age is a strong risk factor for osteoporotic fractures[23, 107]. We did not adjust for bone-active drugs. The data were analysed both with and without participants using these drugs, with no significant differences in the results. This was also done in Paper III. As with other variables retrospectively collected, the participants might have had problems remembering or knowing what kind of drugs they were using.

Paper III

The control subjects were matched on month of examination due to the factor of Norwegian climatic sun exposure. Unfortunately, as described earlier, other sources of sun exposure were not investigated. Thus, vitamin D could have been unnaturally high in some of the patients and controls, which could have been a confounding factor in this paper. Low BMI may be an indicator of insufficient nutritional status and vitamin D inadequacy. Moreover, low BMI is associated with increased fracture risk in both genders[123-125, 205]. High BMI appears to be protective against distal radius fracture[117, 126, 206]. However, nutritional status was not investigated in this study. In any case, the confounding factors we investigated are known risk factors for osteoporotic fractures[121-125, 151-154, 205, 207]. Cigarette smoking is associated with increased risk of osteoporotic fractures[151, 152], but not with distal radius fractures[152]. Cigarette smokers are generally leaner than non-smokers, which can affect BMD[151, 152], and low BMD is a risk factor for fractures[36, 104, 105]. However, lower BMI among smokers has not been found to explain the increased risk of osteoporotic fractures[151]. We decided to make an adjustment for smoking. The analyses were also performed without including smoking and the results did not change significantly.

5.1.5 External validity

Even though many of the patients with distal radius fracture did not participate, one of the strengths in this study was the high number of included patients. In Paper I these fracture patients were included from different parts of Norway (west, south and east), consequently we believe that our findings can be generalised to other parts of the country. However, the prevalence of low BMD and osteoporosis will probably differ somewhat depending on the BMD devices and other factors such as e.g. BMI. Differences in BMD have previously been reported between Northern and Western Norway[204]. Our main conclusion that low-energy distal radius fracture patients aged 50 years and older should be referred to bone

densitometry and evaluated by clinical risk factors, can most probably be generalised. Despite some degree of selection bias, we believe our results in Papers II and III are generalisable, and that distal radius fracture is strongly associated with osteoporosis (Paper II). Other researchers have found similar results in individuals with other types of low-energy fractures[36, 38, 104-106].

Within Norway the prevalence of vitamin D deficiency is found to differ most between ethnic Norwegians and immigrant groups[81]. Only Caucasians were included in Paper II and III. The association between vitamin D inadequacy and distal radius fracture can probably be generalised to other Norwegian regions but not to immigrants living in Norway, nor to distal radius fracture populations in other parts of Europe. The prevalence of vitamin D inadequacy in our material is lower than in studies from other geographical regions[86, 87]. Apart from the different measurement methods used in previous studies, vitamin D status has also been calculated to be higher among Scandinavians than in people from Central Europe[208].

5.2 Discussion of specific results and comparison with other studies

5.2.1 Prevalence of osteoporosis and treatment guidelines (Paper I)

A high prevalence of low BMD (T-score ≤ −2.0 SD) and osteoporosis (T-score ≤ −2.5 SD) among fracture patients indicates the importance of following up these patients with bone densitometry, as these patients benefit from anti-osteoporotic treatment[183-186, 209]. In a substantial proportion of men, including the youngest, anti-osteoporotic treatment was indicated according to Norwegian guidelines. On the other hand, a relatively high proportion of the patients did not have an indication for treatment. BMD is only one of several important factors that contribute to fracture risk, and a high percentage of patients with a high FRAX® score did not have osteoporosis.

Our results on the prevalence of osteoporosis among distal radius fracture patients correspond well with other investigations. In a study from Sweden, 53% of the patients had T-scores < −2.0 SD and 37% had osteoporosis at either the hip or spine measurement site[190]. Another Swedish study showed a prevalence of osteoporosis at 34%[187] at the same

measurement sites. Similarly, in a study from Scotland, 41% of the patients had osteoporosis[191], and in women from Korea, 32% had osteoporosis measured at femoral neck[210]. Both higher and lower prevalence of osteoporosis among distal radius fracture patients are reported; Bahari and co-workers[188] diagnosed osteoporosis at hip or spine in as many as 68% of Irish female distal radius fracture patients. In contrast, only 24% of the British patients in the study by Lashin & Davie[189] were diagnosed with osteoporosis. In men, there are limited data and the results show more variation. In one British study[193] the prevalence of osteoporosis at total hip, femoral neck or spine was higher (42%) than in our study (33%), while in two studies from Scotland[191, 211] the prevalence was lower (23%). Generally, these studies have small numbers of participants compared to our study. Although DXA devices were used, variation in measurement results between individual devices may explain some of the differences. Previous studies have shown the prevalence of osteoporosis and fractures in Scandinavia to be among the highest in the world[20, 49, 50]. Nevertheless, the proportion of distal radius fracture patients with osteoporosis does not seem to be higher in Norway compared to other populations.

Following publication, our results initiated a debate about recommended clinical practice. In agreement with Blank and co-workers (Appendix 1), our results indicate that follow-up of distal radius patients is important. However, a relatively high proportion of the patients with distal radius fractures in our study did not have indications for treatment for osteoporosis. The main statement by Blank and co-workers is that a low-energy fracture is the key manifestation of osteoporosis regardless of BMD, thus a low-energy fracture is synonymous with osteoporosis. In our response letter (Appendix 2) to Blank and co-workers we argued that evidence-based medicine should be the leading principle in treatment decisions. There is no evidence for the effect of drug treatment in reducing the fracture risk in patients with normal or slightly subnormal T-scores. However, we know that BMD is only one of several important factors contributing to skeletal fragility, and our FRAX® results indicate that those patients with normal BMD have as high a risk for subsequent hip fractures as patients with low BMD. Based on this, we agree that clinical risk factors have a high impact in addition to BMD. So far, DXA is the "gold standard" for the non-invasive diagnosis of osteoporosis[42, 60], and BMD is the single best predictor of osteoporotic fractures[36, 104]. Hopefully, in the future alternative techniques for the imaging and quantifying of bone strength, together with advanced methods of imaging bone quality, will be available for routine clinical use. We

concluded that referral to bone densitometry should be done consistently in these patients, to offer treatment to patients with osteoporosis or BMD values close to osteoporosis, but also to identify patients with normal BMD whom we believe to have no need for osteoporosis medication.

5.2.2 Distal radius fracture and osteoporosis (Paper II)

The prevalence of osteoporosis was significantly higher in distal radius fracture patients than in matched controls. Osteoporosis was found to be an isolated risk factor for distal radius fracture in both women and men. The results from this paper support our conclusion in Paper I. Although distal radius fractures are not as strongly associated with increased mortality as hip fractures[53], those patients with low BMD have an increased fracture risk, and an increased severity of the distal radius fracture has been observed[212]. As the follow-up of such patients is generally low[8-10, 213], an alteration of current practice is necessary.

There are few studies on distal radius fracture patients and matched controls. However, our results are in accordance with a Spanish study where 19% of the female distal radius fracture patients were diagnosed with osteoporosis measured at total hip compared to 6% of the control subjects[192]. Contrary to our findings, osteopenia and osteoporosis were only significant in the youngest age-group (≤ 65 years). In an Irish study[188], as many as 68% of the female distal radius fracture patients had osteoporosis at either the total hip or spine measurement site compared to 28% of the controls. In male distal radius fracture patients only one study with a control group was found[193]; in UK patients the prevalence of osteoporosis at femoral neck (37%) was higher than in our male patients (17%). Their controls had a lower prevalence of osteoporosis (9%) than our controls (13%). In regression analysis low BMD was associated with distal radius fracture after adjustment for age and BMI[193]. DXA measurement was used in all studies, but still variation in measurement results may occur. The numbers of participants vary and different regression methods were used, as well as adjustment for different risk factors.

5.2.3 Distal radius fracture and vitamin D inadequacy (Paper III)

We found an inverse relationship between vitamin D levels and distal radius fracture. The results remained significant after adjustment for BMD, BMI, and smoking. However, only a

few distal radius fracture patients had severe or moderate vitamin D deficiency (25(OH)D < 25 nmol/L). Previous data suggest that 25(OH)D levels above 75 nmol/L are beneficial for several health outcomes including fracture, fall prevention, BMD, and extremity strength[78]. Thus, an increased focus on distal radius fracture patients to identify risk factors will lead to preventive treatment for both osteoporosis[5, 214] and vitamin D inadequacy[93].

Previous studies investigating the association between vitamin D inadequacy and distal radius fractures are few. In a Dutch study[87] the proportion of female and male patients with low BMD (T-score ≤ −2.0 SD) and 25(OH)D levels below 50 nmol/L was much higher (69%) than in our patients with osteoporosis (34%). However, the prevalence of osteoporosis was similar to our results (58% versus 51%, respectively). In male distal radius fracture patients from Northern Ireland[86] the vitamin D inadequacy (< 50 nmol/L) was 49% compared to 33% in our study. In the latter study the prevalence of osteoporosis was lower (11%) than in our study (18%). This may be explained by the lower mean age of the Northern Irish participants compared to our study (54 years versus 65 years). As already mentioned, relatively high levels of vitamin D are also found in other groups of patients from Scandinavia with osteoporosis[215]. As the sun exposure in Scandinavia is relatively low, one theory is that the high intake of cod liver oil[208, 216] which increases vitamin D levels, might also increase the risk of fractures. The previously high vitamin A content in cod liver oil[143] has been postulated to have a negative effect on BMD, thus increasing fracture risk[143, 147, 148]. This high level, which was above recommended values, has now been reduced. However, in a large case-control study from Denmark, high doses of vitamin A was not associated with increased fracture risk[150].

6. Conclusions

In the present study we found a relatively high prevalence of low BMD and osteoporosis in distal radius fracture patients. Furthermore, a substantial proportion of patients with a high FRAX® score, and a substantial proportion of patients aged 75 years and older did not have osteoporosis. Hence, referral to bone densitometry and examination of potential risk factors seems to be a good strategy in order to identify patients with distal radius fractures in need of anti-osteoporotic treatment. So far, there is no evidence that anti-osteoporotic treatment prevents new fractures unless osteoporosis is present.

Osteoporosis was associated with distal radius fracture in both women and men after adjustment for confounding factors. The prevalence of osteoporosis was significantly higher in the female patients compared to matched control subjects. In addition, vitamin D inadequacy was associated with distal radius fractures in both genders. The variations in vitamin D levels between patients and controls were independent of differences in BMD, BMI, or smoking history. Hence, bone densitometry, vitamin D samples, and examination of risk factors for osteoporosis should be performed in all patients aged 50 years and older with a low-energy distal radius fracture. These examinations could be integrated in the normal clinical routine to facilitate adequate anti-osteoporotic treatment thus preventing more serious fractures (e.g. hip fracture) in later life.

7. Future research

Follow-up studies of the distal radius fracture patients and the matched controls from Bergen will be performed. The hip fracture risk among distal radius fracture patients and controls will be assessed and the implications of BMD levels will be investigated. Adherence to treatment guidelines will be investigated by coupling our data with the Norwegian Prescription Register.

An extensive randomised controlled trial is needed to investigate whether radius fracture patients with normal or slightly reduced BMD will benefit from anti-osteoporotic treatment. Treatment with bisphosphonates is potentially harmful and risk benefit analyses are needed before new indications are established. Future research should also aim to assess other parameters associated to bone strength to clarify the mechanism of fragility in patients with a low-energy fracture and normal BMD, e.g. peripheral quantitative computed tomography (pQCT)[217]. Studies should also seek further clarification on the effect mechanisms of vitamin D on bone and the possible negative consequences that extensive use of calcium supplements might have in the treatment of osteopenia and osteoporosis.

8. References

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9. Errata

Paper I. Fig. 1: In textbox; T-score <= −1.0 SD should be T-score >= −1.0 SD

10. Appendices

Appendix 1: Perspective. ”Evidence-based” or ”logic-based” medicine?

Appendix 2: Letter. ”Evidence-based” or ”logic-based” medicine?: response to Blank et al.

Appendix 3: Information letter and questionnaire for distal radius fracture patients.

Appendix 4: Information letter and questionnaire for control subjects.