Risk factors for fracture and fracture severity of the distal radius and ankle.

What about osteoporosis, celiac disease and obesity?

Anja Myhre Hjelle

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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CONTRIBUTORS

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We have also collaborated with The Department of Orthopedic surgery and the Department of Radiology at the District Hospital of Førde, The Departement of Rheumatology at Haukeland University Hospital, Bergen, and The KB Jebsen Coeliac Disease Research Centre, University of Oslo.

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Vetvika, Bremanger. Foto: Ingeborg Sol Fure

ABBREVIATIONS

AO	An acronym for the German “Arbeitsgemeinschaft für Osteosyntesefragen”, the predecessor of the AO Foundation
BMD	Bone mineral density
BMI	Body mass index
CD	Celiac disease
CRF	Clinical risk factor
DXA	Dual-energy X-ray absorptiometry
D-W	Danis-Weber classification of ankle fractures
EU27	Refers to the 27 countries of the European Union
FABB	«Forekomst Av Beinskjørhet og Blodprøvemarkør på cøliaki hos pasienter med distal radius- og ankelbrudd i Sogn og Fjordane»
FRAX®	WHO fracture risk assessment tool
GFD	Gluten free diet
TG2	IgA antibody against Tissue Transglutaminase 2
IPAQ	International Physical Activity Questionnaire
T-SCORE	Number of SDs by which BMD in an individual differs from the mean value expected in healthy young women

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I. Hjelle, AM, Apalset E, Mielnik P, Bollerslev J, Lundin KEA, Tell GS: "Celiac disease and risk of fracture in adults- a review". Osteoporosis Int. 2014 Jun; 25(6): 1667-76

II. Hjelle, AM, Apalset E, Mielnik P, Nilsen RM, Lundin KEA, Tell GS: "Positive IgA against transglutaminase 2 in patients with distal radius and ankle fracture compared to community-based controls". Scand J Gastroenterol, 2018 Oct-Nov; 53(10-11): 1212-1216

III. Hjelle, AM, Gjertsen JE, Apalset E, Nilsen RM, Tell GS, Lober A, Mielnik P: "No association between osteoporosis and AO classification severity of distal radius fractures: an observational study of 289 patients". BMC Musculoskeletal Disorders, 2020 Dec; 21(1): 811

IV. Hjelle, AM, Gjertsen JE, Apalset E, Nilsen RM, Tell GS, Mielnik P: "Associations of overweight, obesity and osteoporosis with ankle fractures". Submitted to Osteoporosis International, 26.02.21

ABSTRACT

Background

Fractures are a substantial burden for both individuals and society. For the individual it leads to pain, reduced quality of life, disability and increased mortality. For society, it carries a great cost and requires substantial resources. With the increasing age in the population, this burden is expected to increase. There is potential to prevent more fractures than we do today by increased knowledge about groups at risk and individual risk factors, both through awareness, case finding in defined populations, and targeted treatment in the case of osteoporosis.

Aim

The overall aim of this thesis is to contribute to better fracture prevention through increased knowledge of risk factors and patient groups at risk, focusing on celiac disease, osteoporosis and obesity as risk factors for peripheral fractures.

Materials and methods

The dissertation is based on a case control study of consecutive patients with acute ankle- or distal radius fracture treated at the Helse Førde Hospital Trust in Norway, March 2014- January 2017, and community-based controls.

Results

Our findings are presented in four papers. The first paper is a review on celiac disease and risk of fractures in adults. Previous studies performed on the subject were heterogeneous and difficult to compare, but the overall findings indicate a positive association between celiac disease and risk of fracture. We concluded that adult patients with celiac disease should be considered for bone densitometry in order to estimate fracture risk, thus enabling fracture prevention.

In the second paper we report the prevalence of positive IgA transglutaminase 2 (TG2), a marker for both subclinical and clinically active celiac disease, and celiac

disease in patients with distal radius or ankle fracture compared to community-based controls. We found that 2.5 % of the fracture patients had positive TG2, compared to 1 % in the control group, but the results did not show significantly increased odds of fracture. This study indicates that universal screening for celiac disease in fracture patients is not warranted, but that diagnostic tests should be performed in case of additional factors present increasing the patients' risk of having celiac disease.

The aim of the study reported in the third paper was to determine whether radiographic complexity of a distal radius fracture can be used to see if different distal radius fracture subtypes differ with regard to the prevalence of osteoporosis. When classifying the fractures according to the AO-classification system, we found no association between the severity of distal radius fractures and osteoporosis, hereby challenging a common perception that such an association exists.

The study reported in the fourth paper investigated associations of overweight, obesity and osteoporosis with ankle fracture and the Danis-Weber (D-W) ankle fracture classification. We concluded that overweight increased the odds of ankle fractures and the odds of sustaining an ankle fracture with possible instability (D-W type B and C). Osteoporosis did not significantly increase the odds of ankle fracture, nor the odds of an instable distal fibula fracture.

Conclusion

Understanding the impact common medical conditions such as osteoporosis, celiac disease and obesity have on fracture risk is important in order to identify and treat people at risk. This dissertation aims to expand the knowledge in this research landscape, look into and challenge the perception of common clinical beliefs, and contribute to the path towards new clinical practice guidelines for clinicians.

SAMMENDRAG PÅ NORSK

Bakgrunn

Beinbrudd utgjør en stor belastning både for individ og samfunn. For den det rammer, fører brudd til smerte, redusert livskvalitet, potensielt også til uførhet og økt mortalitet. Ressursbruken i samfunnet er enorm. Parallelt med økende aldring i befolkningen, forventes en betydelig økning i bruddforekomst, og dermed også i den økonomiske og menneskelige belastningen. Økt fokus på og kunnskap om risikofaktorer kan forebygge flere brudd enn tilfellet er i dag, både hos enkeltindivid og på gruppenivå. Det finnes effektive medikamenter som kan redusere bruddrisiko ved diagnostisert osteoporose, som er den sterkeste risikofaktor for brudd, bortsett fra kvinnelig kjønn og økende alder.

Mål

Hovedmålet med denne avhandlingen er å bidra til bedre bruddforebygging i daglig klinisk praksis gjennom økt kunnskap om pasientrelaterte risikofaktorer for brudd, med fokus på cøliaki, osteoporose og overvekt.

Kilder og metode

Avhandlingen er basert på en case kontroll studie som inkluderte pasienter med akutt brudd i ankel eller distale radius, behandlet i Helse Førde i perioden mars 2014 til januar 2017, samt kontroller fra Sogn og Fjordane fylke.

Resultater

Resultatene presenteres i 4 artikler. Den første artikkelen var en oversiktsartikkel som omhandler cøliaki og risiko for brudd hos voksne. Studiene på dette feltet var ulike både i design, metodologi og størrelse, og er vanskelige å sammenligne. Det er likevel tilstrekkelig kunnskap til å konkludere med en positiv assosiasjon mellom cøliaki og bruddrisiko. Konklusjonen i vår oversiktsartikkel er at voksne pasienter med cøliaki

bør vurderes for beintetthetsundersøkelse, og bruddforebyggende behandling igangsettes dersom indisert.

I den andre artikkelen undersøkes prevalens av positiv IgA transglutaminase 2 (TG2), en blodprøvemarkør for både subklinisk og aktiv cøliaki, og cøliaki hos pasienter med distalt radiusbrudd eller ankelbrudd sammenlignet med kontroller uten brudd. 2.5 % av bruddpasientene hadde positiv TG2 sammenlignet med 1 % i kontrollgruppen, men konfidensintervallet var stort. Vi konkluderer med at generell serologisk screening for cøliaki hos alle bruddpasienter ikke er indisert, men at terskelen for å analysere TG2 bør være lav dersom det er tilleggsfaktorer som gjør at cøliaki mistenkes.

Den tredje artikkelen belyser hvorvidt radiografisk kompleksitet av et distalt radiusbrudd kan si noe om sannsynligheten for osteoporose. Vi grupperte radiusbruddene ved hjelp av et klassifikasjonssystem fra vanlig klinisk praksis (AO), og konkluderer med at det ikke var en sammenheng mellom økende kompleksitet i følge AO grupper og større odds for osteoporose. Vi utfordrer dermed en eksisterende oppfatning om en slik mulig sammenheng.

I den fjerde artikkelen ser vi på faktorer som gir økt risiko for ankelbrudd. Vi ser også på faktorer som påvirker plasseringen av den distale fibulafrakturen etter Danis-Weber klassifikasjonen. Studien viser at overvekt øker risiko både for ankelbrudd og for instabilitet av ankelbruddet (økt risiko for D-W type B og C sammenlignet med A). Osteoporose ga ikke sikkert økt risiko for ankelbrudd eller bruddinstabilitet.

Konklusjon

Å forstå hvordan vanlige medisinske tilstander som osteoporose, cøliaki og overvekt påvirker bruddrisiko er viktig for å kunne identifisere de med økt risiko, og dermed behandle og forebygge brudd. Denne avhandlingen bidrar til økt kunnskap på dette vide forskningsfeltet, og utfordrer vanlige oppfatninger om faktorer som innvirker på bruddrisiko. Et mål med avhandlingen var også å bidra til utviklingen av nye praktiske retningslinjer til daglig bruk og nytte for klinikere.

1. INTRODUCTION

Fractures lead to increased risk of death, pain and disability for the individual, and cause an enormous economic burden for societies [1]. The etiology is multifactorial. Most fractures occur as a result of a fall or other trauma. A fragility fracture is usually defined as a pathological fracture that results from minimal trauma (e.g. a fall from a standing height) or no identifiable trauma at all [2]. Our bodies should be able to sustain a fall from this height without a fracture unless there is an underlying condition causing bone fragility. One in three women and one in five men over the age of 50 worldwide will sustain a fragility fracture. The most common cause of fragility fractures is osteoporosis ("porous bone"). During the past two decades, a range of medications has become available for the treatment and prevention of osteoporosis, and these have proved to reduce the risk of osteoporotic fractures. However, there is a big treatment gap, as most patients still do not receive pharmacological intervention according to current recommendations for osteoporotic fracture prevention [3].

Most fractures occur in individuals without osteoporosis [4], and fracture prevention measures therefore need to look beyond this specific risk factor. In order to prevent fragility fractures, we need increased knowledge and awareness concerning individuals and patient groups at risk. Active case finding, both in daily clinical settings and by society-based measures, can enable us to better prevent fractures. Subsequently, both disability, impaired quality of life and shortened life span for the individual, as well as the pressure on the health care systems can be reduced.

Design by Runar Hovland, for the FABB-study

1.1 Fractures in adults

A fracture occurs when a bone encounters an outside force that exceeds its strength. Distal radius, hip, humerus, ankle and vertebral fractures are among the most frequent fracture types in the adult population. According to the Swedish fracture registry's [5] 2018 annual rapport, for men over the age of 60, hip fractures constituted 30.5 % (11 393 patients), fractures of the hand and distal radius 18.2 %, and ankle fracture 8.4 % of the fractures. For women over 60 years, the most frequent fracture was distal radius fracture with 21.0 % (19 357 patients), followed by hip fracture (25.3 %), proximal humerus fracture (11.7) and ankle fracture (7.8%). A peripheral fracture may lead to hospitalization, surgery, immobilization and disability, which again leads to increased morbidity and mortality [1].

Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, also called low energy trauma [6]. The main risk factors for fragility fractures are higher age, previous fracture, female gender, low bone mineral density (BMD), reduced bone quality, underweight, early menopause, smoking, excess alcohol-use, heredity, ethnicity, physical inactivity, falls, medical conditions and effects and/or side effects of medical treatment [7]. Regarding peripheral fractures, osteoporosis especially increases the risk of fracture of the hip [8] and the distal radius [9], and risk factors for fracture differ according to the various fracture sites in the body. When it comes to e.g. the ankle, it has not been clearly demonstrated that BMD or other bone quality related factors increase the risk of fracture (addressed in section 1.6), and there is a complex interplay with both external factors and individual biomechanical factors.

1.2 Fragility fracture burden world wide

Osteoporosis causes more than 8.9 million fractures annually worldwide, approximately 1000 per hour [1]. 3.5 million fragility fractures were sustained in the 27 countries of the European Union (EU27) in 2010, comprising 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures [1]. The economic burden of incident and prior fragility fracture in EU27 was

estimated to € 37 billion. Overall, women have about twice as high a risk of sustaining any fracture than men, but there are variations between different fracture sites. Two to three times as many women as men sustain a hip fracture, but the 1-year mortality rate for men is twice as high [10-13], possibly related to higher rates of comorbidity. Sustaining a fracture, depending on fracture type, may increase the risk of a secondary major osteoporotic fracture of the hip or vertebrae [14].

There is a large difference in the incidence of fragility fractures worldwide, most pronounced in the case of hip fractures. The differences between countries are much greater than the differences in incidence between sexes within a county [15]. Fracture rates are higher in the western world than in other regions, and more than one-third of all osteoporotic fractures in the world occur in Europe [16]. Although there are some differences in the prevalence of osteoporosis between countries, they are quite small [17-19], indicating that the difference in fracture risk cannot solely be explained by differences in BMD. The risk factors for osteoporosis (e.g. underweight, low calcium intake, low exposure to sunlight, early menopause) do not explain differences in risk between countries either [1]. To illustrate the complexity, hip fracture rates in Norway are more than double that of Spanish women [1]. A small study found that Norwegian women had a significantly *higher* BMD than comparable Spanish women, but had a greater height (can increase the impact on bone in case of a fall). They also had impaired bone material properties [20]. Overall, the factor found to best predict the incidence of a major fracture in a population, is socioeconomic prosperity [21]. This may in turn be related to low levels of physical activity [21]. It still remains to fully understand which factors are responsible for the heterogeneity of fracture risk.

The Scandinavian countries have some of the highest incidences of hip fractures in the world [15]. In Norway, despite declining incidence rates [22, 23], the absolute number of fractures is still increasing because of a growing number of older individuals [24]. A recent study estimating the future burden of hip fractures in Norway [25], indicates that health loss lost to hip fractures will approximately double, from 32,850 DALYs (disability adjusted life years) in 2020 to 60,555 in 2040. In addition, there is no trend towards decreasing incidence of a second hip fracture, indicating that secondary

fracture prevention needs to be improved [22]. Since hip fractures are a late consequence of osteoporosis with serious consequences for the patients, awareness of increased fracture risk should be addressed before the hip fracture, or another major osteoporotic fracture, occur.

1.3 Concepts of bone, osteoporosis and bone mineral density

Our bones are in a state of continuous remodeling to ensure their flexibility and stamina, and bone is a living, active tissue. Bone mass increases in youth until peak bone mass is reached (approximately 20 to 30 years of age), followed by a stable period in middle age [26, 27]. When the process of bone resorption (through the action of the osteoclasts) is dominant over the bone formation (action of the osteoblasts), the net result is bone loss over time. A gradual decrease in bone mass starts in women at approximately 50, and in men at about 65 years of age. The decrease becomes pronounced in women at menopause because of the loss of estrogen [28]. These changes in bone mass with aging are demonstrated in *Figure 1*:

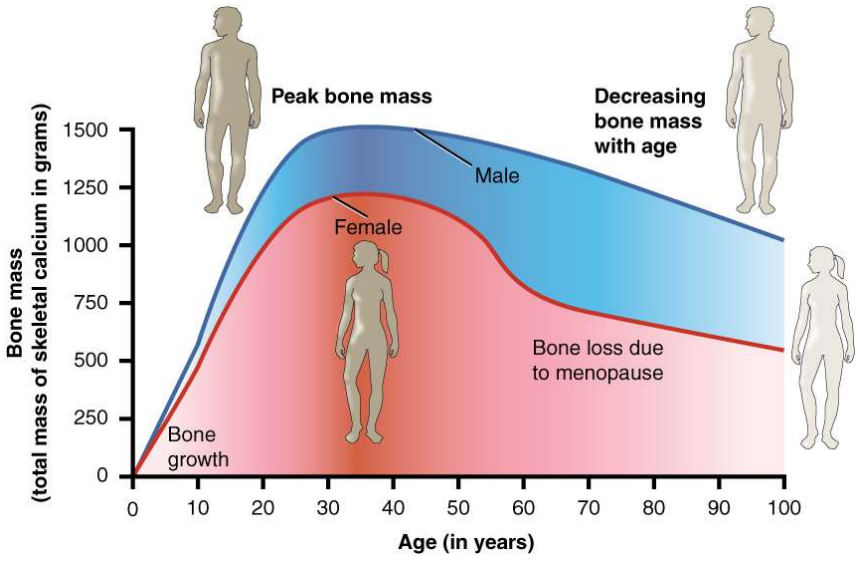

Figure 1: Relationship between age and bone mass in men and women [29].

The two basic types of bone are cortical and trabecular bone. Cortical bone forms the compact outer shell of all bones and the shafts of the long bones. It supports weight, resists bends and twists, and accounts for about 80 % of the skeletal mass in adults. Trabecular bone is the latticework structure within the bones that adds strength without excessive weight. It supports compressive loading in the spine, hip, and calcaneus, and it is also found at the ends of long bones, such as the distal radius [30].

Osteoporosis is defined as "a disease characterized by low bone mass, micro architectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk" [31]. According to The IOF (International Osteoporosis Foundation), the number of individuals aged 50 years and older with osteoporosis was 20 million in 2015 [32], hereunder approximately 7 % of men and 22.5 % of women.

In 1994 and 2008, the WHO published classification criteria for osteoporosis in postmenopausal women based on the T-score for BMD, defining osteoporosis as a T-score less or equal to 2.5 standard deviations (SD) or below the young female adult mean BMD [33]. Osteopenia is defined as a T-score between -1.0 and -2,5 SD below the mean, and normal bone mineral density as a T-score equal or better than -1 SD below the mean (*Figure 2*).

T-score ≥ -1	Normal BMD
T-score < -1 and > -2.5	Low bone mass/osteopenia
T-score ≤ -2.5	Osteoporosis

Figure 2: T-score definitions of bone mineral density [33].

Ideally, the definition of the skeleton's strength should also include parameters other than BMD, such as microarchitecture and geometric features, but this is not yet applicable for daily clinical practice. BMD is most commonly defined as the amount

of bone mass per unit area (areal density, g/cm^2) [34]. The most widely used technique to measure BMD is dual energy x-ray absorptiometry (DXA) [35]. The principle is to use two different photon energies of the x-ray beams to optimize the differences in the x rays' attenuating effects on soft tissue and bone [36]. The absorption of x-rays is very sensitive to calcium content in tissue. DXA provides a two-dimensional areal value, and is thus influenced by bone size as well as true density. DXA has the advantages of low radiation dose, being ease to use, having a short scan time, providing high-resolution images, high precision, and stable calibration. The most commonly measured sites are the lumbar spine (L1-L4) and the proximal femur, but also the radius and the whole body can be evaluated. The lumbar spine may be impaired by degenerative changes, vertebral deformities and extra-skeletal calcifications especially in the elderly, making the femoral neck the standard reference site for diagnosis [37].

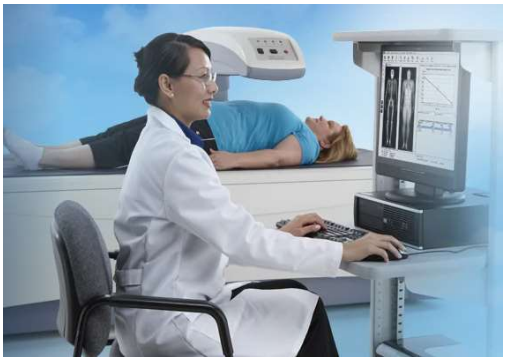

Figure 3: DXA Lunar Prodigy, GE. Permission by GE Healthcare Norge.

1.4 Preventing fractures in adults

General management to prevent fractures is a multifaceted task. Most fractures occur as a result of a fall, making fall prevention measures essential, especially in the elderly. Focusing on modifiable factors that increase the likelihood of fall is of essence. Impaired vision is a good example, as treatment of cataracts has been proven to reduce falls [38]. Other modifiable individual factors include exercise to improve

balance and skeletal health, ensuring adequate diet, avoiding age-related weight loss (hereunder loss of muscle mass), avoidance of smoking and excessive alcohol intake, and reducing the use of sedatives [1]. Environmental factors that can precipitate a fall in home dwellers include slippery flooring, loose carpet edges, inadequate footwear, and, on the society level, slippery roads and sidewalks, and difficult access to community services such as stores and public offices [1]. For institutionalized individuals, external factors such as facilitated modern buildings, appropriate beds and equipment are important in preventing falls. In addition, having a sufficient number of health personnel to assist the dwellers may reduce the risk of falls.

Chronic medical conditions may increase the risk of falls, and optimizing the treatment of the illness at hand is key, e.g. preventing hypoglycemia in diabetics, reducing rigidity in patients with Parkinson's disease, and reducing joint inflammation in patients with rheumatoid arthritis. Concerning inflammatory diseases, maintaining a low inflammatory activity may be beneficial for several reasons. One is that a chronic inflammation over time is a cause of secondary osteoporosis, another is that chronic inflammation may be an independent risk factor for fracture and falls [39].

In the case of osteoporosis, there are pharmacological interventions widely available that effectively reduce fracture risk, and that have also been proven cost-effective. A combined supplement of calcium and vitamin D is beneficial for patients with osteoporosis, but the results on fracture rate reduction have been variable. Some studies have reported a reduction in fracture rate [40, 41], relative risk reductions for hip fracture ranging from 0.81-0.87 [42]. Vitamin D deficiency has also been linked to increased risk of falls. It may act as a driver of chronic inflammation, and the cause-effect discussions when it comes to vitamin D deficiency and fractures are extensive [43]. A bisphosphonate (preferably oral alendronate, alternatively intravenous zoledronic acid) is usually the drug of choice when targeted treatment is indicated, but also denosumab, raloxifene, strontium ranelate, teriparatide and romosozumab are in current use for the treatment of osteoporosis for both postmenopausal women and men [44]. They are proven effective in preventing fractures, both as primary prevention, and as secondary prevention of the next major osteoporotic fracture [45-52]. There are

no head-to-head studies with fracture as the primary outcome, so direct comparison between agents is challenging. Generally, the reduction rate in vertebral fractures is larger than the demonstrated efficacy in preventing non-vertebral fractures [52]. The difference in fracture-preventing effect according to the fracture site can reflect the various drugs' different effects on cortical and trabecular bone, but also the importance of falls in the pathogenesis of fractures. A limitation of the drug approving studies is that most large studies investigate fracture prevention in postmenopausal women with primary osteoporosis, and extrapolation of the results to other populations has its shortcomings.

Despite effective medication being available, most individuals having sustained an osteoporosis-related fracture or who are at risk of such a fracture, remain untreated [53-55]. A recent study from eight countries across Europe found that 75 % of elderly women seen in primary care who were at high risk of fragility fractures were not receiving appropriate medication [56]. In Denmark, the gap between women eligible for antiosteoporotic treatment and those actually receiving treatment after a fracture remained stable at 88-90% in the 2005 to 2015 period [57]. In order to diminish this treatment gap, fracture liaison service models are effective measures, and are proven to be both cost-effective and to reduce mortality [58, 59]. Ortogeriatric care models are associated with higher rates of diagnosing osteoporosis and starting treatment. However, whether orthogeriatric care prevents subsequent falls and fractures, is not clear [60]. These initiatives are, however, mainly based upon preventing a second fracture from occurring, and are not suitable for primary prevention of osteoporotic fractures.

1.5 Distal radius fractures

In Norway, the annual around 15 000 distal radius fractures [61] constitute approximately 20 % of all fractures in adults [62]. The incidence is approximately four times higher in women than in men [63]. The prevalence of distal radius fracture in Norway is one of the greatest in the world, and is more than double the prevalence in e.g. the United States of America [64, 65].

The most common fracture of the distal forearm is the Colles' fracture, caused by a fall on the outstretched arm, resulting in a dorsal misalignment [66]. If the patient falls with the hand in a flexed position, this will result in a fracture with a volar displacement, called a Smith's fracture [67]. In addition to the distal radius, distal forearm fractures may also include a fracture of the ulna styloid process. Although such fractures are rarely fatal, the consequences are often underestimated, as the occurrence of a wrist fracture increases the odds of a clinically important functional decline in women by almost 50 % [68]. A recent study from the National Swedish fracture register found an overall 1-year mortality of 2.9 % after a distal radius fracture. In adults, the most typical patient is an elderly woman sustaining the fracture through a simple fall in her own residence [63].

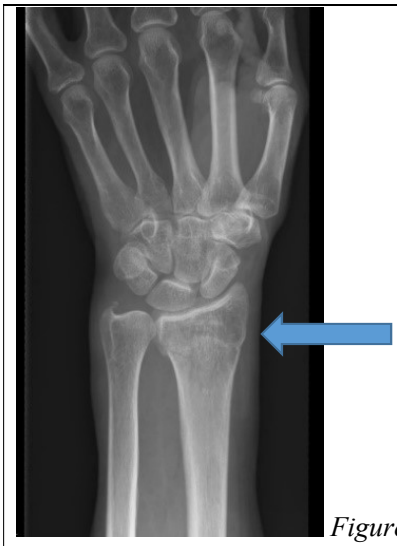

Figure 4: Müller AO type A2 fracture (study participant)

Distal radius fractures are closely related to low BMD [9], and are considered as osteoporotic index fractures since such patients have a higher risk of a major osteoporotic fracture later in life [69, 70]. A recent study found 86 % reduced risk of subsequent hip fracture after distal radius fracture in a 4-year follow up when active osteoporosis care was initiated [71]. A distal radius fracture in post-menopausal

women is recommended to lead to further evaluation with DXA and preventive measures for secondary fractures [72].

The most common radiological classification system of distal radius fractures in clinical practice is the Müller AO-system (AO) [73]. The Müller AO classification classifies fractures according to localization and fracture pattern [74]. Each fracture is given two numbers to describe which bone is affected and where in the bone the fracture occurs. A distal radius fracture is classified as 23. This number is followed by a letter describing the joint involvement; Type A is extra articular, type B is partly articular, and type C completely articular, supplemented further by division into subgroups. A simplified graphic of this is illustrated in *Figure 5*:

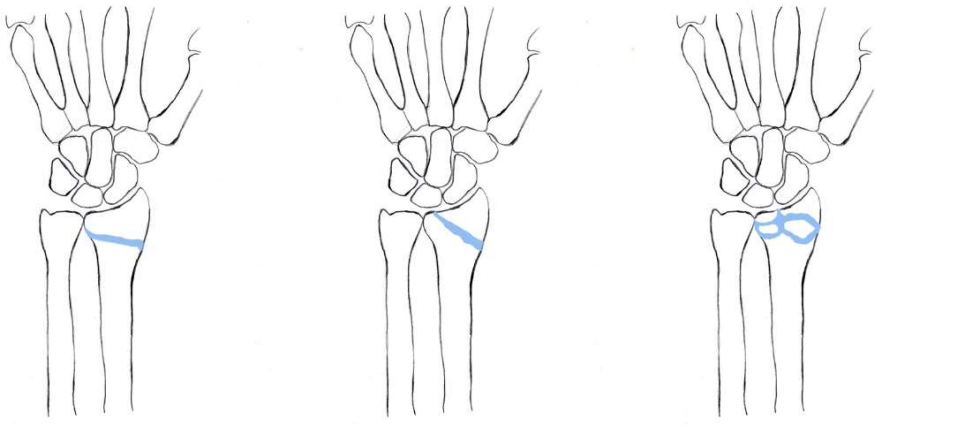

Figure 5: The Müller AO classification of distal radius fractures.

Design by Eir Pétursdóttir

1.6 Ankle fractures

An ankle fracture affects the distal tibia (shinbone), the distal fibula (outer bone of the lower leg), or both. The most common type of ankle fracture is a break of the lateral malleolus: the lower part of the fibula [75]. Ankle fractures constitute approximately every tenth fracture in adults [76, 77]. Ankle fractures are, in contrast to distal radius fractures, not considered to be classical osteoporotic fractures. Compared to patients with osteoporotic fractures of the hip, spine, and distal radius, patients sustaining an ankle fracture are typically younger [78], and have a higher BMI (body mass index) [79]. However, it has been shown that postmenopausal women with an ankle fracture have an increased risk of subsequent fracture [80], and approximately two thirds of the ankle fractures in adults result from a low-energy trauma [76].

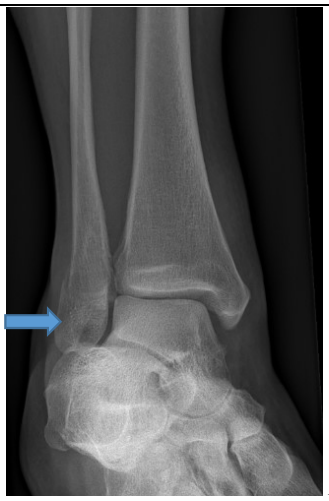

Figure 6: D-W type B fracture (study participant).

A commonly used classification of lateral malleolar fractures is the Danis-Weber classification (D-W) [81]. D-W type A fractures occur below the level of the ankle syndesmosis, leaving the syndesmosis and the deltoid ligament intact. The medial malleolus is occasionally fractured. Type B fractures are situated at the level of the ankle syndesmosis, the medial malleolus may be fractured, and the deltoid ligament may be torn, resulting in variable stability. Type C fractures occur above the level of the syndesmosis, the deltoid ligament is always torn, causing instability of the ankle joint and requiring internal fixation. This is illustrated in *Figure 7*:

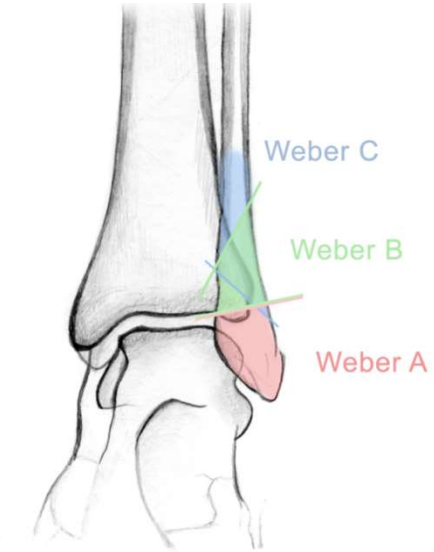

Figure 7: The Danis-Weber classification of ankle fractures (types A, B and C).

Type A: fracture of the lateral malleolus distal to the syndesmosis (usually stable).

Type B: fracture of the fibula at the level of the syndesmosis (variable stability).

Type C: fracture of the fibula proximal to the syndesmosis (unstable).

Design by Eir Pétursdóttir

1.7 Osteoporosis and risk of fracture

It is highly relevant to make a distinction between the definition of osteoporosis based on BMD versus clinical findings; the occurrence of fragility fractures. Elderly persons with fragility fractures of the hip or vertebrae should be considered for osteoporosis treatment independent of the result of a DXA scanning. The indication for pharmacological treatment is hence not made on the basis of the BMD measurement alone, but is based on the patient's individual fracture risk. This is in line with principles of treating other diseases, e.g. hypertension. The diagnosis is based on measurement of blood pressure, and the aim of treatment is to prevent stroke and

congestive heart disease over time. So, “normal” for age does not mean that the condition should not be treated, if the risk of complications is high. Large population-based studies show that the risk of fracture increases by a factor of 1.5-3.0 for each SD decrease in BMD [8]. This means that the ability of BMD to predict fracture is comparable to the use of blood pressure to predict stroke [1]. There are, however, substantial differences between countries in how cost-effective treatment for osteoporosis is, due to the large differences in fracture risk in different populations [82]. It is also important to recognize that BMD alone has high specificity, but low sensitivity, meaning that the majority of osteoporotic fractures will occur in individuals with osteopenia or normal BMD [83].

There are a large number of additional risk factors that provide information on fracture risk independently on both age, sex and BMD [1]. Particularly, it is important identify risk factors that are amenable to modification. The following clinical risk factors (CRFs) form the input to the fracture probability tool FRAX®: age, sex, low body mass index, previous fragility fracture, parental history of hip fracture, glucocorticoid treatment (≥5 mg oral prednisolone daily for 3 months or more), current smoking, alcohol intake 3 or more units daily, rheumatoid arthritis, and other established causes of secondary osteoporosis (hypogonadism, inflammatory bowel disease, prolonged immobility, organ transplantation, type I diabetes, thyroid disorders and chronic obstructive pulmonary disease) [84]. FRAX® models weigh these CRFs and estimate the 10-year probability for hip fracture or a major osteoporotic fracture, with or without a BMD T-score, according to which country the patient resides in [85]. This tool is widely used in daily clinical practice, and is a good supplement when treatment decisions are to be made. The probability of fracture calculated from FRAX® depends upon age and life expectancy as well as the current relative risk. Thus, where the risk of death is high, the probability of fracture will decrease for the same fracture hazard. Using FRAX®, men and women of the same age and the same BMD have similar fracture risk [84]. The somewhat higher probabilities in women are due to the longer life expectancy in women compared with men. A major limitation is that several of the CRFs used in FRAX® take no account of dose-response, but rather represent an average dose or exposure vs. non-exposure [1]. Additionally, there are CFRs not

incorporated in FRAX® that are very important when it comes to a person's risk of fracture, the most apparent being previous falls. Furthermore, a range of other clinical conditions (e.g. celiac disease, irritable bowel syndrome, psoriasis and psoriatic arthritis, systemic lupus erythematousus, Parkinson's disease) increase the risk of fractures [86-90]. This increased fracture risk is partly mediated by osteoporosis, but also by mechanisms like chronic inflammation and increased risk of falls. Correspondingly, medication other than glucocorticoids also increase fracture risk (e.g. sedatives [91], some antiepileptics [92], aromatase inhibitors [93]). For this reason, there is a need to further assess additional individual CRFs when attempting to estimate a patient's fracture risk as accurately as possible.

1.8 Celiac disease and risk of fracture

Celiac disease (CD) is an immune-based enteropathy characterized by malabsorption, small intestine villus atrophy, and antibodies to transglutaminase. CD is triggered by exposure to wheat gluten and similar proteins in rye and barley, and affects genetically susceptible persons [94]. It is a common disease, especially in Scandinavia, Ireland, and the United Kingdom, with a prevalence of 1.0-1.5 % [95]. The incidence of CD is increasing over time [96-99]. CD, both undiagnosed [99], diagnosed but untreated, and even when treated with a gluten-free diet (GFD), is associated with a small, but statistically significant increased mortality [100, 101]. This is probably due to the fact that CD gives an increased risk of several comorbidities, such as lymfoproliferative malignancy, type 1 diabetes and other autoimmune diseases, as well as osteoporotic fractures [102]. CD was classically considered to be a childhood illness, presenting as malnourished children due to malabsorption, with short statue and failure to thrive. However, presentation of CD in adult age is now more common, and subtile and atypical presentations represent a substatinal clinical challenge. The majority of patients with CD remain undiagnosed [103, 104], and, importantly, undiagnosed adult patients have a reduced quality of life [105].

CD affects almost exclusively individuals expressing the human leukocyte antigen (HLA) haplotype DQ2 or DQ8, which displays an inflammatory T-cell mediated

immune response against gluten. These haplotypes, however, occur in about 40 % of the general population, so it is not sustainable as a sceening tool [106]. But a negative test if CD is suspected in a specific patient, will in the everyday clinical setting render active CD or an increased risk of developing the disease highly unlikely. CD might be suspected due to symptoms, to increased risk because of defined comorbidities (e.g. dermatitis herpetiformis, DM type 1, autoimmune thyroid disorders, Sjogrens syndrome) or because of familiy history of CD. However, there are cases of CD with negative serology, so if the clinical suspicion is high, duodenal biopsy should still be performed [94]. Why some of the HLA-DQ2/-DQ8 carriers develop CD, while the majority does not, is not fully explained, but we know that additional genetic and environmental factors are involved. For example, viral infections play a central role in CD pathogenesis [107].

The major environmental factor responsible for the development of CD is gluten, a protein consisting of alcohol-soluble prolamins (which carry most of the antigenic properties) and insoluble gluteins [108]. The prolamine in wheat is called gliadin. CD patients mainly react to specific sequences in wheat gliadins, but also homologous sequences in rye (secalins) and barley (hordeins). In adults, a biopsy from the duodenum displaying architectual disturbance (e.g. villous flattening and crypt epithelial hyperplasia) and abnormal amount and distribution of various celltypes (e.g. increased number of plasma cells in the lamina propria, increased number of intra-epithelial lymphocytes) is required for the diagnosis [94]. The degree of histologic pathology is graded with the Modified Marsh Classification [109]. The higher the Marsh score, the more serious the disease, with more pronounced symptoms, risk of comorbidities and morbidity. Low BMD in adult CD patients has also been found to be directly associated with histologic severity [110].

The enzyme tissue transglutaminase (TG) plays a major role in the immune response to gluten [111]. The expression of TG increases during intestinal tissue damage, and can be found both in analyses of blood samples, and in intestinal biopsies in patients with CD. The first line screening test for CD is the IgA antibody against transglutaminase 2 (TG2) [94]. This is a test with a high sensitivity and specificity

[112, 113]. In children with positive HLA DQ-2/DQ-8 and malabsorptive symptoms, TG2 > 10 times upper limit is considered diagnostic, and intestinal biopsy is not required [114]. Spontaneous positive to negative seroconversion has been observed in children. This indicates that celiac autoimmunity might be transient, and subsequently, that serology might overestimate the prevalence of celiac disease in population based screening studies. However, the same phenomenon occurs very rarely in adults [104]. It is important to also analyze Immunoglobulin A (IgA). IgA deficiency is 10 to 15 times more common in patients with CD than the general population, and individuals with IgA deficiency may have a false negative TG2 [115]. For both the duodenal biopsy and the serologic tests to be reliable, the patients have to be on a gluten-containing diet. Elevated TG2 combined with Marsh score 2 or 3 is consistant with CD, whereas Marsh grade 0 or 1 is categorized as potential CD (and a higher risk of developing CD later) [94]. A commonly used model to illustrate the CD spectrum is the iceberg-model [116], as depicted in *Figure 8*.

The visible peak above the water line represents the group with clinical manifestations of CD, both gastrointestinal symptoms (e.g. chronic diarrhea, abdominal pain, weight loss) and extra-intestinal symptoms (in adults e.g. dermatitis herpetiformis, fatigue, artralgia, osteoporotic fractures, neurological symptoms, infertility in women). The patients in the visible part of the celiac iceberg also have the characteristic histological changes in the small intestine, as well as elevated TG2, and they are HLA-DQ2/DQ8 positive. The first submerged part of the iceberg represents the patients who have the same findings on biopsy, serology test and are HLA-DQ2/DQ8 positive, but they have no or minimal symptoms. The lowest part of the iceberg consists of people who share the same genetic markers, and have a positive TG 2, but have little or no symptoms, and the intestinal biopsy is normal. This status is referred to as “latent” or “potential” CD [116].

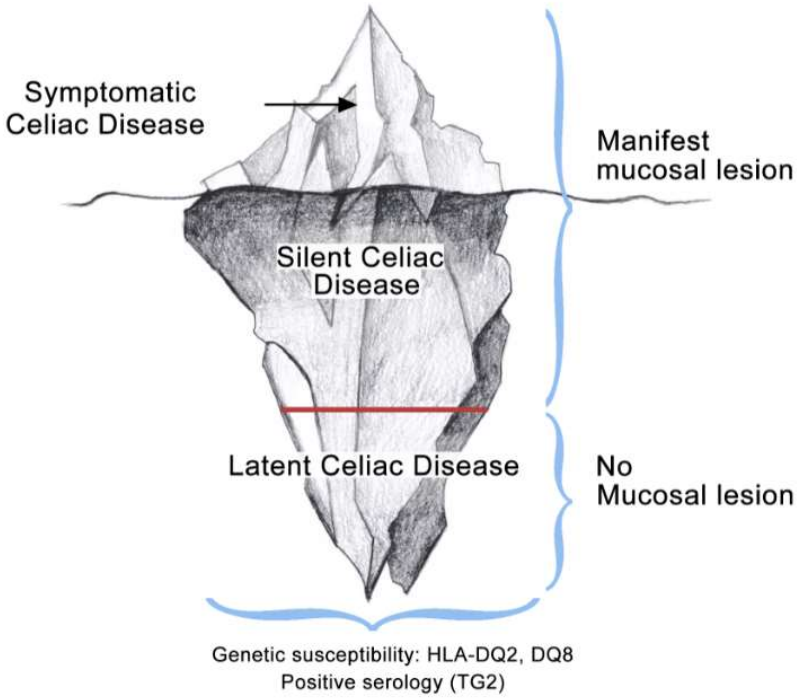

Figure 8: Celiac disease iceberg model. Originally from Bozzola et al, 2014, Celiac Disease: An Update [116]. *Design by Eir Pétursdóttir.*

Over the recent years, interest in the interplay between autoimmunity and bone metabolism has increased, and we are now aware of both direct and indirect interactions between antibodies and bone cells, in particular osteoclasts [117]. The role of TG2 in CD is one example where autoantibodies constribute to localized or systemic bone loss, another example is the role of anti-citrullinated protein (anti-CCP) in rheumatoid arthritis [118]. Even though the characteristics of the autoimmune disease itself (e.g. malabsorption, inflammation, immobility, glucocorticosteriod treatment) is perceived as the main cause of poor bone health in these patients, autoimmunity itself is thought to be a direct trigger. In the case of CD, the prevalence

of osteoporosis in newly diagnosed adult patients is significantly higher than in the general population, affecting up to 70 % when other comorbidities are correlated for [119, 120]. Malabsorption, vitamin D and calcium deficiencies are identified as the probable main factors leading to low BMD in CD. Patients with CD may also have a secondary lactose intolerance resulting from decreased lactase production by the damaged villi [121]. However, CD patients without signs of malabsorption also have a lower BMD compared to the healthy population [122]. Chronic inflammation with subsequent loss of integrity in the intestinal mucosal immunity, vitamin D insufficiency, deficiency of growth factors and increased intestinal permeability ("leaky gut") are possible causes of low BMD in CD patients without evident malabsorption [120, 123-125].

Furthermore, autoimmune mecahnisms, e.g. autoantibodies against osteoprotegerin (OPG), which inhibits bone resorption, may contribute to development of osteoporosis in patients with CD [117, 126]. RANKL is the key mediator for osteoclast proliferation, and activates RANK, stimulating the differentiation of precursors into mature osteoclasts with bone-resorbing activity [127]. The clinical importance of the OPG/RANKL/RANK system is demonstrated by the anti bone-resorptive fracture-preventive drug denosumab, a monoclonal antibody against RANKL. Furthermore, TG2 itsself belongs to a family of enzymes catalyzing a Ca^{2+}- dependent acyl-transfer reaction in which new γ-amide bonds are formed, relevant to bone calcification [128]. This may play a direct role in modulating maturation of bone/cartilage matrix, facilitating the final mineralization of osteoid into bone tissue [129].

Osteoporosis is not the only factor leading to increased risk of fractures in adult patients with CD. Structural alterations of bone tissue impairing the mechanical quality [130, 131], reduced neuromuscular function increasing the risk of falls are also important aspects. There is an increased risk of fracture associated with the initial diagnosis of CD in adult patients [132]. Once treatment with gluten-free diet is initiated, the fracture risk seems to diminish [133, 134]. The younger the patient when starting the treatment, the better the response [135]. This indicates that early detection and treatment of CD is important in order to avoid fractures. The studies previously

performed regarding celiac disease and fracture risk are scarse, heterogenous, and difficult to compare [86, 132-134, 136-143].

Findings from cross-sectional studies suggest that low BMD and osteoporosis are more common in individuals with elevated anti-TG2 levels [143-145]. In a large retrospective study, low BMD only occurred in the CD patients with increased TG2 levels [146]. The existing literature does not conclude whether the increased fracture risk in adult CD patients is substantial enough to consider a case-finding strategy, performing TG2 analyzes on fracture patients with no other obvious cause of fracture.

1.9 Obesity and risk of fracture

Obesity is a global epidemic, and worldwide, 44 % of adults now fulfill the diagnostic criteria for overweight or obesity [147]. Most of the world's population live in countries where overweight and obesity kill more people than underweight and malnutrition. More than 1.9 billion adults were overweight in 2016, and of these, over 650 million had obesity [147]. According to the 2020 report on global obesity from the World Bank Group, Norways has the fourth highest prevalence of obesity in Western-Europe [148]. The Nord-Trøndelag Health Study (HUNT) reported an obesity prevalence of 23 % in 2006-2008 compared to 13 % in 1984-1986 [149].

Body mass index (BMI) is a simple index of weight-for-height (kg/m^2), used to classify overweight (BMI greater than or equal to 25) and obesity (BMI greater than or equal to 30) in adults. High BMI is a major risk factor for premature death, cardiovascular diseases, diabetes, musculoskeletal disorders (especially osteoarthritis) and some cancers, as well as disability and reduced quality of life [147, 148], as illustrated in *Figure 9*:

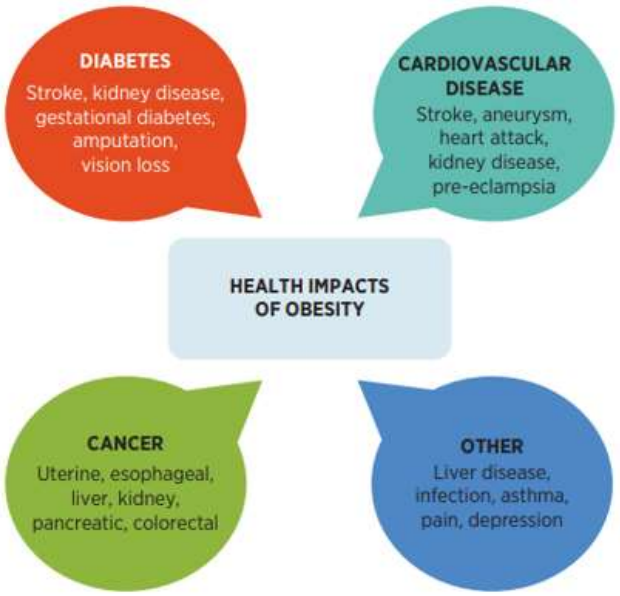

Figure 9: "Obesity: Health and Economic Consequences of an Impending Global Challenge". Shekar, Meera and Barry Popkin, 2019.

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Individuals with obesity have traditionally been considered protected against osteoporotic fractures. A larger body mass induces greater mechanical loading on bone, with a consequent increase in BMD to accommodate the greater load [150]. Indeed, large epidemiological studies have previously shown that high BMI is positively correlated with increased BMD and reduced risk of fragility fractures [151]. However, when the mechanical loading effect is removed, both fat mass and body fat percentage are negatively correlated with BMD [152-154], and obesity is no longer considered to be protective against fractures [155]. Especially fractures at bone sites with a large proportion of cortical bone, such as the upper arm or ankle, are positively correlated with obesity [156, 157]. Fractures in individuals with obesity are asociated

with greater morbidity than in the general population [158]. This may be due to e.g. technically challenging surcial procedures, higher risk of postoperative complications, and a longer and more complex convalescent phase.

It has been reported that although BMD is significantly higher in obese women with fractures than in their non-obese counterparts, obese women with fracture have a significantly lower BMD compared with women of similar age and weight without fractures [155]. This may lead to an underestimation of fracture probability by fracture algorithms such as FRAX®, since obese individuals have higher BMI and BMD [159].

There are several potential mechanisms for affecting bone health and leading to increased risk of fragility fractures in obese individuals. Obesity can be considered a chronic inflammatory state, with increased proinflammatory cytokine production and insulin resistance induced by viceral fat deposits [160]. There is a higher prevalence of vitamin D insuffiency in individuals with obesity. However, this is likely to reflect greater volume of distribution of vitamin D into fat, muscle and extracellular fluid. Therefore, serum 25OH-vitamin D may not reflect the whole-body vitamin D status in obesity [158]. Other potential risk factors for osteoporotic fractures in individuals with high body weight are secondary hyperparathyroidism, hypogonadism, calcium malabsorption, comorbidities and co-medications [151].

Obesity affects several hormones known to act on bone. For example, circulating levels of adiponectin are inversely related to BMD [161], and could modulate RANK/RANK-ligand/OPG signalling [162]. Higher serum parathyroid hormone levels are reported in obese individuals, which can potentially have negative effects on cortical bone [163]. On the other hand, we know that high subcutaneous fat mass can be protective against fractures, both through loading mechanisms, but also mediated via the aromatase expressed by adipocytes, leading to higher levels of circulating estradiol [158]. In addition to the effect overweight and obesity have on BMD and bone quality directly, there are several other factors to consider that may lead to a greater risk of falls with subsequent fractures. Even though individuals with overweight have relatively more muscle mass with possible beneficial effects [164],

intramuscular fat content is associated with poorer muscle function and postural instability, and subsequently increased risk of falls [158].

There is an inverse association between accumulation of body fat and decreased muscle mass and/or function, a fenomenon recognized as sarcopenic obesity [165]. Sarcopenic obesity leads to increased inflammation as part of the metabolic syndrome, and to impaired and altered regeneration of skeletal muscle cells. It may also be of relevance to distinguish between high adiposity and high BMI. A Swedish study found high degree of adiposity to be more common than BMI-defined obesity in elderly, and does not provide similar protection from osteoporosis and sarcopenia [166].

There is a substantial overrepresentation of hyperglycemia and diabetes type 2 (DM2) in individuals with overweight. Both DM 2 itself and the medical treatment of DM2 causes disturbances in the serum glucose making patients more prone to falls [167]. Further, greater biomechanical forces during a fall, twist or turn due to higher body weight, can lead to fractures at different sites compared to individuals with BMI within the normal range. Individuals with overweight or obesity tend to fall more backwards and sideways, thus e.g. the wrist is less exposed, whereas the ankle, humerus are femur are more exposed [155]. The ankle has little soft tissue padding, making it a vulnerable fracture site compared to other sites in patients with obesity.

1.10 Case-finding to prevent fracture

Fracture risk is multifactorial, and a broad approach is necessary to prevent as many fractures as possible. Even though we have extensive knowledge concerning many risk factors, there are still several preventable, modifiable and treatable risk factors of which both society and health professionals are not sufficiently aware. Understanding how various chronic diseases modulate fracture risk is important to both identify and treat people at risk. Increased knowledge will enable clinicians to perform case finding in a daily clinical setting on the basis of assessing individual risk factors, as well as health care systems to perform case finding through targeted screening programs on group levels where indicated. Clear guidelines with a high degree of concordance of recommendations would reduce confusion as to who is in need of fracture preventing

measures, and thereby contribute to narrowing the osteoporosis treatment gap [168]. Public campaigns increasing patient awareness are also very important. The patients at risk may appear in different clinical settings, not only in the osteoporosis clinics, but at their primary physician, the orthopedic ward, the gastroenterologist, or elsewhere. This will increase the opportunity to identify and treat modifiable risk factors for fracture before the fracture occurs.

1.11 Rationale for the present study

In order to reduce the fracture burden, there are many risk factors to consider. The importance of early detection and treatment of osteoporosis is recognized as an effective primary fracture preventing measure. Primary osteoporosis, as a result of an interplay between genetics, age and sex, can be treated with increased/adjusted exercise, optimization of diet and supplementary calcium and Vitamin D, in addition to effective fracture preventing medication. In secondary osteoporosis, where the cause of osteoporosis is another medical condition or medication, it is essential to treat the disease responsible for the reduced bone quality, in order to limit its negative effect on bone. The earlier the condition causing osteoporosis is diagnosed and treatment initiated, the better the fracture preventing effect will be. However, most fractures occur in people without osteoporosis, and fracture etiology comprises so much more. Fracture preventing case finding strategies needs to look beyond the BMD-values, and fracture prediction tools like FRAX® do not take into account all relevant risk factors.

With this background, the aim of the current study was to better assess risk of fracture in daily clinical practice in three chosen settings where official guidelines are lacking or not agreed upon:

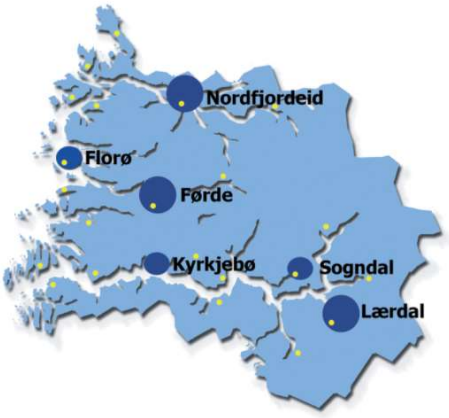
1) Patients with CD
2) Individuals with overweight or obesity
3) Radiologically defined fracture subgroups

We looked at two different peripheral fracture types. Distal radius fractures, which we know are closely related to osteoporosis, and ankle fractures. Ankle fractures were

chosen because the literature was inconclusive on ethiology and the high prevalence. We also wanted to compare and study the contrast between these two types of fractures.

The Norwegian authorities have stated that research is one of the main tasks of public hospitals, and that all health trusts in Norway are obligated to do research alongside patient care. Establishing strong research environments can be a challenge for small health trusts and hospitals, with limited resources both financially and when it comes to research support systems, as well as having few specialized physicians within the same profession. At the same time, we also found these same challenges to be advantages. The treatment of patients and the clinical research go hand in hand, the number of medical professionals involved are few, making the system effective and reliable. Cooperation between different professions is easy to achieve, because of compact personnel groups and the clinicians being used to working with a wide range of medical issues and challenges. We wanted to strengthen the research network in Helse Førde, and build an extensive database and biobank for multi-purpose use. We designed the database with the potential of later national and international collaboration in mind, and wanted to collect data comparable to studies performed elsewhere in Norway.

Sogn & Fjordane county (from January 2020 part of Vestland county) is an interesting region in which to perform patient oriented clinical research. In the mid-1970s, Sogn & Fjordane was included in the National Health Screening Service due to its favorable characteristics with respect to cardiovascular morbidity, life expectancy and health behaviors. The county spans an area of 18,623 km^2, holds approximately 110,000 inhabitants, and the society is predominantly rural.



Sogn & Fjordane, Helse Førde institutions

In Norway, Sogn & Fjordane has had the longest-lived population for decades. The lifestyle of the population has been characterized by moderation and adherence to traditional values, and the divorce rate, consumption of alcohol, prevalence of daily smoking and crime rate have been low compared to other regions of Norway [169]. And even though the regional differences within the country seem to diminish over time [170, 171], still, life expectancy at birth was in 2002-2016 found to be 0.6 years longer in Sogn & Fjordane than in Norway in general for men, and 1.2 years longer for women [172].

Higher rates of hip fracture and all fractures combined have been observed in urban compared to rural areas in Norway [173]. Studies by Omsland et al have shown differences in hip and forearm BMD measurements in rural compared to urban areas, and urban women have an increased risk of forearm fractures compared to rural women [174, 175]. This research originates from NOREPOS (The Norwegian Epidemiologic Osteoporosis Studies [176], sub studies within large population-based surveys in four districts in Norway (Tromsø, Nord-Trøndelag, Hordaland and Oslo), which are also linked to big epidemiological research groups in Scandinavia. The collaboration with NOREPOS has been a source of expertise to lean on, and allowed us to develop our own team with quality and assurance, and to expand our national and international network.

2 AIMS

Overall, this dissertation sought to explore risk factors for peripheral fractures in adults, in order to improve target case-finding strategies in daily clinical practice as a fracture prevention measure.

The specific aims were:

Paper I:

1) To summarize existing knowledge concerning the risk of fracture in adult patients with celiac disease (CD)

2) To provide clinicians with increased knowledge on how to evaluate the potential risk of fracture in CD-patients, and which patients should be referred to DXA scan

Paper II:

1) To investigate the prevalence of positive TG2 and celiac disease in patients with distal radius or ankle fracture compared to community based controls, in order to see if patients with peripheral fractures had greater odds of CD compared to healthy controls

2) To advice clinicians about whether fracture patients ought to be screened for suspected CD

Paper III:

1) To determine whether radiographic complexity using the A0-classification of distal radius fractures can be indicative of osteoporosis

2) To prove or disprove if the radiographic severity of distal radius fracture can be used by the clinician to decide which patients should be referred for fracture risk assessment and/or treatment to prevent secondary fractures

Paper IV:

1) To investigate associations of overweight, obesity and osteoporosis with ankle fractures compared to controls without previous fractures

2) To investigate associations of overweight, obesity and osteoporosis with ankle fracture subgroups according to the Danis-Weber classification

3 MATERIALS AND METHODS

3.1 Study design

The FABB-study ("Forekomst Av Beinskjørhet og Blodprøvemarkør på cøliaki hos pasienter med distalt radius- og ankelbrudd i Sogn og Fjordane") is a case-control study designed with the main objective to investigate whether adult patients suffering a distal radius or ankle fracture had a greater prevalence of celiac disease compared to healthy controls. To our knowledge, no previous case control studies with this aim have been conducted. The main exposure was known or undiagnosed CD (with positive TG2 as the marker), and the main outcome was the occurrence of fracture of the distal radius or ankle. The sample size was calculated during the study planning phase using a conventional test for difference in proportions. We assumed a CD prevalence of approximately 1 % in the control group and 3-5 % in the case group, according to the best available estimates [95, 120]. However, during enrollment, we needed to adjust to the daily clinical setting and available resources, and make sure that our osteoporosis clinic could manage the inclusion of study patients without this affecting standard patient care. Having patients with distal radius fractures referred to DXA-scanning was indicated also according to current secondary fracture preventing guidelines. We therefore aimed to include participants with a 2:1 ratio of cases and controls (400 patients and 200 controls), thus yielding the FABB-study underpowered to conclude in some aspects. However, the research questions we aimed to address with this study also consisted of several other factors, affecting the final design.

Starting from January 2012, after a 6 months planning phase, we had several information meetings with physicians, nurses and health secretaries at the orthopedic departments in The Helse Førde Trust, both at Førde Central Hospital, as well as the hospitals in Nordfjordeid and Lærdal. We wanted to ensure that the recruitment of fracture patients was evenly distributed from all the municipalities, in the same manner as the planned community-based controls would be. There were posters with information in the relevant waiting areas (*Appendix 1*), and nurses and secretaries helped to remind new interns and physicians to ask patients if they wanted to participate in the study.

3.2 Study population and participation rates

3.2.1 Cases

From March 1, 2012 until January 13, 2017, 400 consecutive patients age 40 or older permanently living in Sogn & Fjordane county with an acute distal radius fracture or ankle fracture were referred to the rheumatology outpatient clinic, after being asked to participate by physicians at the orthopedic departments (*Table 1*).

Inclusion criteria	Exclusion criteria
≥ 40 years of age Recent fracture of a) Distal radius b) Ankle (all involving the lateral malleolus, including those affecting the medial malleolus) Able to give informed consent	< 40 years of age Trimalleolar fracture Not able to give informed consent

Table 1: Inclusion and exclusion criteria for the fracture patients.

The ankle fractures had to involve the lateral malleolus. Trimalleolar ankle fractures were not included because of an assumed higher likelihood of high-energy trauma, including traffic accidents. We included both patients with low energy fractures (equivalent to a fall from standing height or lower) and fractures due to traumas with higher energy. The majority of patients were invited to participate in the study at the first contact with the orthopedic outpatients clinic, others at later planned controls or at the time of planned day surgery of the fracture. Still, after the first year of inclusion, we discovered that some patients who were eligible for participation had not been asked, resulting in a revision of the procedure. In addition to the existing referral system, the head of the orthopedic department delegated to two orthopedic interns to go through lists of patients with

the relevant ICD-10 codes, to make sure that all those eligible to participate in the study, were in fact asked. If this was not mentioned in the patients' medical charts, the intern called and asked the patient if he or she had been previously informed about the study, and, if not, if they wanted to participate. This was done on a monthly basis. If the patient wanted to participate, he or she was referred to the rheumatology department. We then sent a letter with detailed information about the study (*Appendix 2*), two copies of the consent form (*Appendix 4*), and the questionnaire (*Appendix 6*). In this letter, the patient was informed that he/she would receive an appointment at the rheumatology outpatient clinic at Førde Central Hospital within 4-8 weeks. We aimed to coordinate the appointment with a planned follow up visit at the orthopedic outpatient clinic, to avoid excess travel for the patient.

3.2.2 Controls

We requested the Norwegian Population Registry to identify controls. After having included approximately 100 fracture patients, we asked for lists of randomly selected controls from all municipalities in Sogn & Fjordane, in the following age cathegories: 40-49 years, 50-59 years, 60-69 years, 70-79 years and 80 years and older, asking for 2/3 women and 1/3 men, and double the numbers we aimed to include in the study, e.g 200. As planned, we later asked for a second withdraw, at a time when we were then able to adjust according to the age- and sex-distribution of cases so far included.

Inclusion criteria	Exclusion criteria
≥ 40 years of age Able to give informed consent	Not able to give informed consent Previous fracture (except fingers or toes)

Table 2: Inclusion and exclusion criteria for the controls.

We mailed a letter with detailed information about the study (*Appendix 3*), two copies of the consent form (*Appendix 4*), and the questionnaire (*Appendix 6*). In this letter, the individual was informed that he/she would receive a notice with an appointment at the rheumatology outpatient clinic at Førde Central Hospital within 4-8 weeks. Despite information given on previous fractures being an exclusion criteria, some of the controls who accepted the invitation turned out to have had previous fractures, and could not be included. If these persons wanted, they were still examined with DXA-scan and received appropriate follow up, but were not enrolled in the study. For the controls, all examinations were free of charge. The controls were included during the same time period as the cases to best assure true comparability of the DXA-results and serum analyzes.

3.2.3 Participation rate

In order to include 400 fracture patients in the study, 780 consecutive fracture patients fulfilling the inclusion criteria were invited to participate, yielding a participation rate of 51.3 %. This consisted of 289 included patients with distal radius fracture (516 asked, 56.0 % participation rate) and 108 patients with ankle fracture (264 asked, 40.9 % participation rate). We included 199 controls (the protocol aimed for 200 controls), out of 467 invited (42.6%).

3.2.4 Study outline/flow chart

The study outline, inclusion and the different subgroups of study participants who are included in each of Papers II, III and IV are illustrated in the flow chart presented in *Figure 11*. In Paper II, the 400 primarily included fracture patients are compared to the controls. Two of the 199 controls had stated in the questionnaire using gluten free diet, despite not having celiac disease. This could potentially result in a false negative TG2, and these two controls were therefore excluded. In Paper III, five of the 289 distal radius fracture patients could not be assessed when it came to fracture severity, because of the radiographic images not being performed in Helse Førde, and these were therefore excluded from further analyses.

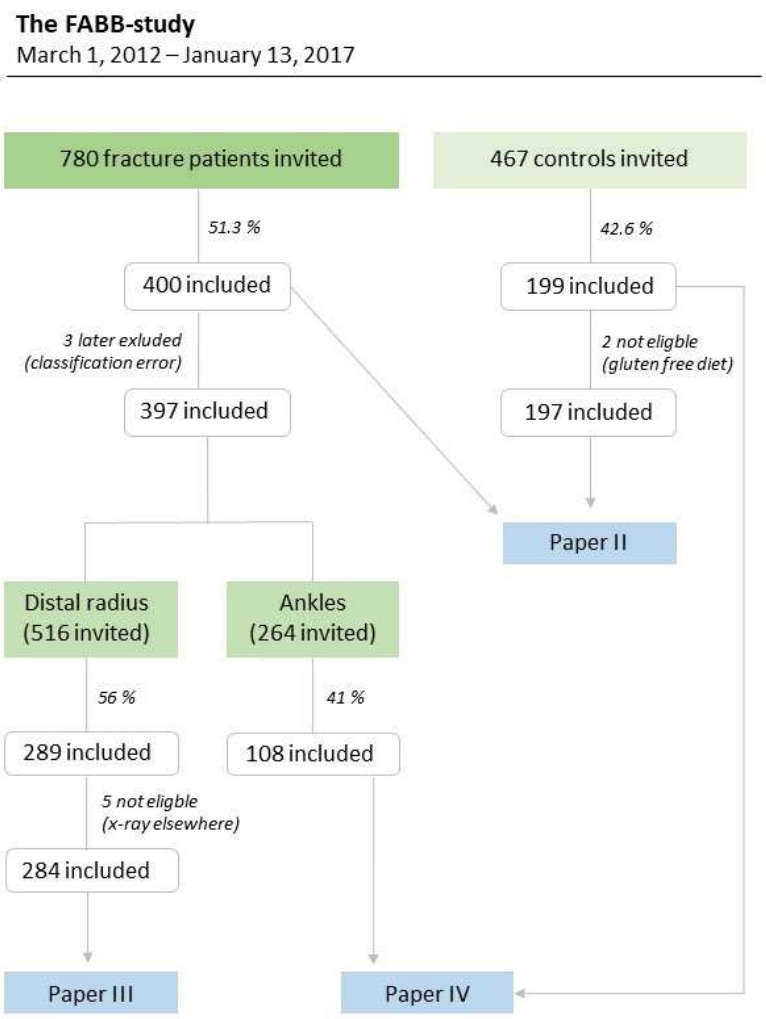


Figure 11: FABB-study Flow Chart

In the process of systematically reanalyzing all x-rays, we discovered patients who had been registered in the database with incorrect information. In the case of the distal radius fracture group, two were misclassified as fractures (these were sprains with no visible fracture line). One patients was registered as a distal radius fracture,

but was in fact a proximal radius fracture of the elbow joint. Three ankle fractures had been registered as distal radius fractures but were ankle fracture patients, and one trimalleolar fracture had been included, even though this was an exclusion criteria. In addition to this, one patient was primarily registered as having both a distal radius fracture and an ankle fracture in the same trauma, however, this ankle fracture was in fact an isolated medial malleolus fracture, and was therefore later exluded from sub analysis.

3.3 Data collection

On the day of examination, the patient or control met one of the two physicians in charge of the study. Information concerning consent, exclusion and inclusion criteria was repeated, and, if the criteria were fulfilled and the patient still wanted to participate, a study number was provided, and the consent form was signed in two copies by both patient/control and physician. The DXA scanning was then performed, and height and weight were measured. A blood sample was obtained and analyzed, and serum and full blood samples were stored in biobank. After these procedures were completed, the patient or control had a consultation with the physician, where the results of the DXA scan and the patient/control questionnaire was reviewed. Appropriate measures to prevent further fracture, or in the case of the healthy controls, primary fracture prevention, was either initiated, or recommended to the participants' general practitioner. Some results of the serum analysis performed and corresponding medical advice was sent to the patient and general practitioner 1-2 weeks after the examination day, because the analysis were performed elsewhere (described in section 3.3.3).

3.3.1 Questionnaire

The participants answered a self-administered questionnaire in the time interval between receiving this by letter, and at the latest, at the day of inclusion. The questions concerned parental and maternal history of fractures, number and fracture history of siblings, diagnosed celiac disease of the participant or first degree relatives, daily intake of milk and cheese, use of vitamin supplements,

hereunder specified calcium, vitamin D and/or omega 3 supplements, the trauma mechanism and month of fracture, age and localization of previous fractures (the questions regarding fractures were removed from the controls' version of the questionnaire), physical activity using the modified IPAQ (International Physical Activity Questionnaire) score, comorbidities, use of gluten-free diet, diagnosed dermatitis herpetiformis, performed duodenal biopsy, daily medication, historic use of glucocorticoids for more than 3 months, current and previous use of tobacco and alcohol, questions regarding abdominal symptoms, and questions concerning age of menarche and menopause, and miscarriages (women) (*Appendix 6*).

3.3.2 BMD

Height (m) and weight (kg) were measured in light clothing without shoes before the DXA examination. BMD was then measured at the femoral neck and total hip at both sides and at the lumbar spine (L1-L4), using GE Healthcare Lunar Prodigy Rtg 5603, manufacture year 2000, with a daily quality assurance of +/- 2 %. The procedure was performed with the participant lying straight on the back. When measuring the lumbar spine, the patient was positioned with the knees in a 90 degree angle using a pillow under the calfs. The hips were measured with the femora straight on the table and rotated 15-25 % inwards, achieved by a spacer placed between the ankles. BMD T-scores were calculated using US National Health and Nutrition Examination Survey (NHANES III) reference population of female Caucasians aged 20-29 years for femoral neck and total hip [177] and Lunar female reference database for lumbar spine.

3.3.3 Laboratory tests

Serum analyses to reveal possible causes of secondary osteoporosis and increased fracture risk were performed, including white blood cell count, hemoglobin, sedimentation rate, serum electrophoresis, ionized calcium, albumin, thyroid-stimulating hormone, parathyroid hormone, 25-OH Vitamin D, alkaline phosphatase, alaninaminotranferase, aspartataminotransferase, ferritin, folic acid, total Ig A and, deaminated gliadin and TG2. TG2 was in 52.1% analyzed with an

ELISA test, 5.7 % by an EliA method (Unicap 100 by Phadia®) and in the remaining 42.2 % by a multiplex flow immunoassay (BioPlex® 2200 Celiac IgA). In addition, in men analyses also included testosterone, lutenising hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH were analyzed using Immulite 2000XpI (Siemens®). TG2, demaminated gliadin and the sex hormone analyses were performed at laboratories at Haukeland University Hospital in Bergen. 25 OH-Vitamin D was for the first two thirds of the inclusion period measured at Haukeland University Hospital, but shifted to Førde Central Hospital when the laboratory there started to perform these analyses. The remaining serum samples were analyzed by the laboratory in Førde Central Hospital.

3.3.4 Radiological examinations

The radiological examinations were performed at one of the three radiologic departments in Helse Førde, located in Førde, Nordfjordeid and Lærdal, according to standard clinical procedure. The examinations were performed with FUJI® XG-1, Simens Luminos Fluorospot Compact FD and GE Healthcare Discovery XR656 (Førde), FUJI® XG-1, detector Canon® CXDI 50 G (Nordfjordeid), FUJI® XG-1, detector Canon® CXDI (Decotron) (Lærdal). The radiographic ankle series included anteroposterior, mortise (with the foot in 10 degrees internal rotation) and lateral radiographs. The distal radius series images comprised standard anterioposterior and lateral radiographs. In September through November 2019, one experienced radiologist reviewed all the x-rays, and classified the ankle fractures according to the Danis-Weber classification and the number of uni- and bimalleolar involvement, and the distal radius fractures according to the AO-classification. In 197 of 289 distal radius fracture patients included (68%), there were additional CT scans available, and these were also reviewed and used as supplementary information when classifying the fractures.

3.4 Statistical analyses

3.4.1 Paper II

Continuous data are described as means and percentages. Associations between categorical variables were calculated using Pearson's chi square test. Associations between CD and fracture are presented in terms of odds ratios (ORs) with 95 % confidence intervals, estimated from logistic regression models. All analyses were performed using IBM® SPSS Statistics version 24, 2016 and R (version 3.4.1 for Mac OS). All *p* values are two-sided, and values < 0.5 are considered statistically significant.

3.4.2 Paper III

Descriptive statistics for age, sex, BMI, number of patients with osteoporosis/osteopenia/normal BMD, and overweight were performed in the distal fracture group. Data between subgroups were compared using chi square or Fisher's exact test for categorical data and two-sample t-test or Mann-Whitney U test for continuous data. ORs were estimated with 95% confidence intervals using unconditional logistic regression models. All p-values are two-sided and values below 0.05 are considered statistically significant. All calculations were performed using R version 3.6.2.

3.4.3 Paper IV

Descriptive statistics for age, sex, height, BMI, osteoporosis, osteopenia, smoking, physical activity, low energy trauma (yes/no), 25-(OH) vitamin D levels and polypharmacy were performed. Data for fracture patients were compared with controls using chi square or Fisher's exact test for categorical data and two-sample t-test or Mann-Whitney U test for continuous data. ORs were estimated with 95% confidence intervals using unconditional logistic regression models. All p-values were two-sided, and values below 0.05 were considered statistically significant. All calculations were performed using R version 3.6.2.

3.5 Ethical concideration

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics (REC West) (*Appendix 7*). All participants signed a written informed consent form on the day of examination.

All referred fracture patients were recommended to have the DXA scan performed if considered clinically indicated, regardless of participation in the study. Advice on dietary supplements, recommendation on treatment with bone-sparing agents like antiresorptives, and advice concerning the indication for a DXA follow up was given to the participants and their primary physician. In the case of positive laboratory tests, e.g. serum electrophoresis with M component or hypercalcemia, the patients were referred to the corresponding specialist (a hematologist or endocrinologist). Patients with positive TG2 were, after being asked if they wanted further examination, referred to the gastroenterology department. All except two participants with positive TG2 had a duodenal biopsy taken, after discussion with the consulting gastroenterologist. This was not part of our study, but standard clinical follow up care.

The screening of fracture patients for CD raises important ethical issues. Universal screening of fracture patients is not recommended, since the prevalence of CD in patients with a recent fracture is unknown, and subsequently, also the cost-benefit of such screening. A study from The Netherlands published in 2020 was the first study where patients at a fracture liaison service (FLS) were systematically screened for CD [178]. The prevalence of CD in this cohort of fracture patients was 0.38 %, and the authors do not recommend standard screening for CD in FLS patients. This knowledge was not available at the time when our study protocol was being designed. The prevalence of CD also varies within Europe, being higher in Scandinavian countries. Systematic prevalence studies in Norway have yet to be performed. A positive TG2 in adults usually leads to the recommendation of further examination with upper endoscopy and duodenal biopsy. The complication rates of upper endoscopy is low, and if complications occur, are most often associated with sedation [179]. Still, however small, as with all procedures, there is a potential risk of serious

complications, e.g. perforation of the esophagus or ventricle. This potential risk must be weighed against the potential benefit of being diagnosed with CD. It has been shown, that even adult and elderly patients with no subjective complaints before diagnosis, reported a better quality of life after starting treatment with gluten free diet [105]. This may be explained by the variety of both common constitutional and gastrointestinal symptoms that untreated CD may express, and such symptoms can easily be accepted by the patient as common complaints and "part of life". In addition, as discussed in section 1.8, the fact that patients with untreated CD have an increased mortality, indicates a potential benefit of targeted screening in groups of people with a perceived higher risk of CD compared to the general population.

Consideration of screening for osteoporosis in postmenopausal women and elderly men with distal radius fractures is recommended, in order to prevent secondary fractures [180-182]. When it comes to ankle fractures, there are no guidelines for referral to DXA scan evaluation. But, the DXA emits very limited doses of x-rays, and does not pose any risk to the participants. It is pain-free, and non-invasive. Still, if ankle fractures are not in fact related to osteoporosis, and do not increase the patients' risk of a later major osteoporotic fracture, it is not ethical to use health resources for this purpose in clinical practice.

Regarding the ankle fracture patients and the control groups, many cases of osteoporosis were revealed, that would have remained undiagnosed, if not for the study participation. This is an ethical dilemma, providing information to the patient on increased fracture risk, and perhaps recommending treatment to decrease this risk, when the patient might, in retrospect, have preferred not knowing. However, in our daily clinical settings, patients usually appreciate the opportunity to prevent a potential fragility fracture from occurring.

4. MAIN RESULTS

4.1 Paper I

Celiac disease and risk of fracture in adults- a review.

We identified eleven relevant original studies published in 2000-2011, where celiac disease was the exposure and fracture the outcome, ten being cross-sectional studies [132-134, 136-142] and one being a case study [183]. The results of the analyzed articles are summed up in *Figure 12*, here also included a metanalysis by Olmos et al [86], including all but three of the papers we include in our review.

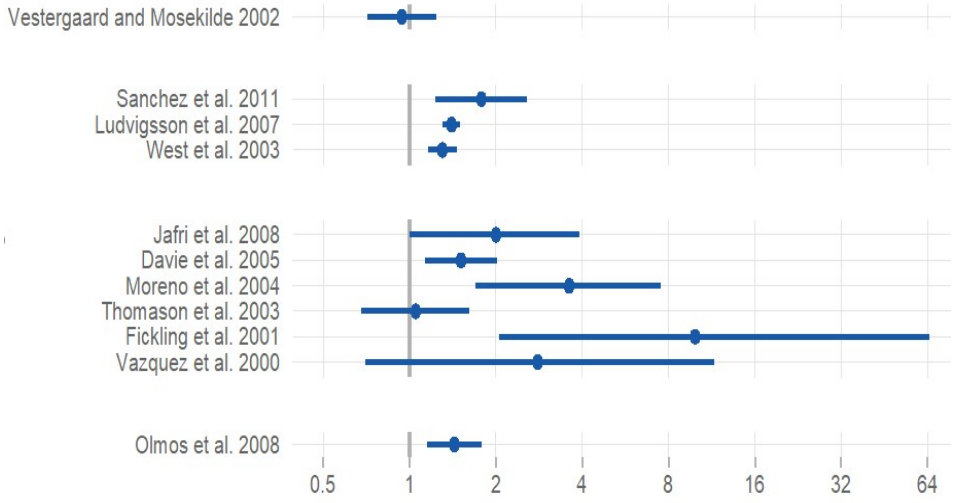


Figure 12: Illustration on reviewed literature in Paper I.

The x-axis shows the Risk Ratio (Vestergaard and Mosekilde), Hazard Ratio (Sanches et al, Ludvigsson et al and West et al) or Odds ratio (all other studied referred) with 95 % confidence intervals. The studies not weighted, and no metaanalysis has been performed.

The included studies were heterogeneous, differing both in design, selection criteria, sample size and the CD entity, and were subsequently challenging to compare. However, the overall findings indicate a positive association between CD and risk of fracture. On the basis of this literature review, we recommended that adult patients

with CD should be referred to bone densitometry for assessment of osteoporosis and evaluation of fracture risk.

4.2 Paper II

Positive IgA against transglutaminase 2 in patients with distal radius and ankle fractures compared to community-based controls.

Twelve participants (10 fracture patients and two controls) had positive TG2, among whom seven had osteoporosis, and the remaining osteopenia. About 2.5 % of the 400 fracture patients had positive TG2, compared to 1 % of the 197 community-based controls, giving an odds ratio of 2.5 for having positive TG2. This difference is not statistically significant, but there is a trend towards positive TG2 being more prevalent in fracture patients than in controls. This supports recommended clinical practice in Norway, which is to be aware of the fact that CD can cause secondary osteoporosis and fractures, and examine patients with CD-serology tests upon suspicion.

The prevalence of osteoporosis was significantly higher in the distal radius fracture group than in the healthy controls and ankle fracture patients.

4.3 Paper III

No association between osteoporosis and AO classification of distal radius fractures: an observational study of 289 patients.

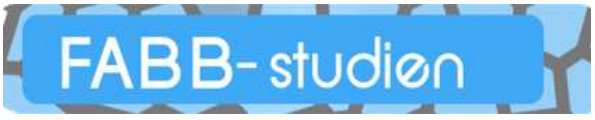
Of 289 distal radius fracture patients aged ≥ 40 years, both male and female, 130 had osteoporosis. The patients with osteoporosis did not have increased odds of a more complex distal radius fracture (defined as AO-classification fracture types B or C compared to type A fractures) compared to patients with osteopenia or normal BMD. Current smoking and a low energy trauma mechanism were associated with less complex fractures (Type A). We concluded that the AO-classification of distal radius fractures cannot be used to decide which patients should be referred to DXA scan and considered for secondary fracture prevention.

4.4 Paper IV

Associations of overweight, obesity and osteoporosis with ankle fractures.

We investigated 108 patients with ankle fractures and compared them to 199 community-based controls without a fracture history. In addition, we investigated the associations of overweight, obesity and osteoporosis with lateral malleolus fracture subgroups according to the Danis-Weber (D-W) classification system.

Overweight increased the odds of ankle fractures and the odds of sustaining an ankle fracture with possible instability (D-W type B or C) compared to the more stable D-W type A fracture. Osteoporosis did not significantly increase the odds of ankle fractures. We conclude that having suffered an ankle fracture does not automatically indicate the need of further osteoporosis assessment.



5. DISCUSSION

5.1 CD and TG2 in patients with fracture

In paper II, we compared individuals with known CD and positive TG2 among the fracture patients to the controls with no fracture history. The subjects with known biopsy verified CD before entering the study, all had negative TG2, indicating compliant treatment to gluten-free diet. In total, 6 subjects with known CD and 12 with positive TG2 participated in the study.

	Sex	Type of fracture	Known CD	Positive TG2	TG2 titer	BMD[5] (DXA[6])	Vitamin D (nmol/L)
C[3]	M		x			osteoporosis	132
C	M		x			osteopenia	54
C	K		x			normal	64
C	K			x	104.9 (<20)	osteoporosis	73.2
C	K			x	32.8 (<20)	osteopenia	45.8
P[4]	K	Radius	x			osteoporosis	55.7
P	M	Radius	x			osteoporosis	49.5
P	K	Radius	x			osteoporosis	75
P	K	Radius		x	42.6 (<20)	osteoporosis	61.2
P	K	Radius		x	58.5 (<20)	osteoporosis	55.3
P	K	Radius		x	24.6 (<20)	osteopenia	63.5
P	K	Radius		x	21.3 (<20)	osteoporosis	117
P	M	Radius		x	79.7 (<20)	osteoporosis	68
P	M	Radius		x	20.5 (<20)	osteoporosis	61.9
P	K	Radius		x	579.7 (<20)	osteoporosis	missing
P	K	Ankle		x	63.1 (<20)	osteopenia	55.6
P	K	Ankle		x	80.9 (<14.9)	osteopenia	59
P	K	Ankle		x	105.0 (<14.9)	normal	109

Table 3: Overview of CD and TG2 positive subjects in the study.

C: controls, P: patients

We did not find any statistically significant difference in the prevalence of CD (diagnosed and undiagnosed) in patients with fractures compared to controls. The statistical power of the study is, however, not sufficient in order to rule out such an association, as discussed in sections 3.1 and 6.4. The results nevertheless indicate that

positive TG2 is more commonly found in fracture patients than in controls. Larger, population-based prospective studies are needed in order to assess if positive TG2 increases the risk of fracture.

As discussed in section 1.8, osteoporosis is considered the main risk factor for the increased fracture risk in CD-patients. In addition, several BMD-independent variables leading to increased risk, such as reduced bone quality, changes in fat and muscle composition, Vitamin D insufficiency, increased risk of falls and other associated autoimmune diseases and their treatment, should also be considered. Most fractures in CD patients seem to occur before the CD diagnosis is made, and in patients who are non-compliant to the gluten-free diet (GFD) [133, 135]. There is a marked and fast reduction in fracture risk after transition to GFD when diagnosed with CD, already statistically significant after a year [184]. This could indicate that factors other than BMD are relevant for the increased fracture risk in CD-patients, the improvement in BMD being a slow process, unless potent pharmaceutical agents are in play. On the other hand, studies have shown significantly increased T-scores as soon as 2 years after starting GFD [143]. Also, a recent registry-based cohort study found that if a CD patient underwent a DXA scan, and the result was included in the FRAX® calculation, CD was no longer a significant risk factor for fracture. When the authors defined CD as a secondary osteoporosis risk factor in FRAX, the same conclusion was made [185]. However, in their analyses, all fractures associated with a trauma diagnosis code were excluded and the control group were selected from patients who did not fulfill the criteria for CD. This raises the concern whether all relevant fractures were actually taken into consideration here, or if the fracture prevalence and the spectrum of fracture risk in CD patients were underestimated.

We do not suggest that all patients with fracture should be screened for CD, as the pre-test likelihood of CD is too small for this to be recommended [94]. We do, however, think that the current threshold for screening upon clinical suspicion should be lowered, at least in countries with a high prevalence of CD. It has been shown, that in addition to significantly reducing the fracture risk after CD has been diagnosed and treatment been initiated, the risk of malignancies is reduced [102] and the quality of

life, even in the elderly, is improved [105]. And the earlier the diagnosis is made, the better the response of initiation of treatment and long-term outcome, both concerning intestinal and extra-intestinal manifestations. The close relationship between CD and other autoimmune diseases has also led to a new research field exploring whether early GDF in TG2 positive individuals, can in fact prevent CD from becoming clinically apparent, and may delay, or prevent, other autoimmune diseases from arising (e.g. type 1 diabetes and thyroid disease) [186].

5.2 Osteoporosis as a risk factor for distal radius and ankle fractures

It is well known that distal radius fractures in adults are closely related to low bone mineral density [9], and that patients sustaining a distal radius fracture have an increased risk of a major osteoporotic fracture later in life [70]. Results of our study also supports such an association, finding that the prevalence of osteoporosis was significantly higher in the radius fracture group (45.0 %) than in the ankle fracture patients (23.2 %) and control group (22.3%) ($p<0.001$). The results were also significant when adjusted for sex and age.

The patients with distal radius fractures and osteoporosis had, compared to those with osteopenia or normal BMD values, a statistically lower BMI, they were older, a higher percentage were women, and there were more current smokers. There was also a significantly higher proportion of low energy trauma causative of the distal radius fracture in the patients with osteoporosis by DXA measurement. All these factors are in line with the notion that distal radius fracture are associated with the same risk factors that we recognize as classical risk factors for osteoporosis. This stands in contrast to the ankle fracture patients, in which the prevalence of osteoporosis was comparable to that in the control group, and osteoporosis did not significantly increase the odds of ankle fracture in our study (crude OR 1.03 (95 % CI 0.58-1.79), adjusted for age and sex OR 1.31 (0.72-2.38), adjusted for age, sex, BMI and smoking status OR 1.65 (0.86-3.14)). Furthermore, there were no significant differences by sex,

smoking habits or trauma mechanism comparing the patients with ankle fracture and osteoporosis to the ankle fracture patients with osteopenia or normal BMD (*Table 4*).

Characteristics	Ankle fractures			Radius fractures		
	Osteoporosis (n)			Osteoporosis (n)		
	Yes (25)	No (83)	*p*	Yes (130)	No (159)	*p*
BMI (kg/m^2) (SD)	25.8 (22.0 to 4.03)	29.5 (20.1-41.8)	<0.001	25.5 (18.4-47.7)	27.1 (17.3-47.2)	0.005
Current smoking	28.0 %	16.9 %	0.39	18.0 %	12.7 %	0.11
Previous smoking	28.0 %	38.6 %	0.61	45.3 %	49.2 %	0.19
Male sex	28.0 %	31.3 %	0.81	12.3 %	25.2 %	0.01
Low energy trauma	76.0 %	69.9 %	0.63	76.9 %	56.6 %	<0.001

Table 4: Characteristics of patients with and without osteoporosis in the ankle- and distal radius fracture groups.

Two sample t-test is used for continuous data (BMI), Chi-squared test or Fishers exact test for count data when applicable.

Results of our study confirm that distal radius fractures are closely related to osteoporosis while ankle fractures are not. Having sustained an ankle fracture, even when occurring at low energy trauma, does not on its own justify a referral to a DXA scan.

5.3 Risk factors for ankle fracture

Ankle fractures were included as one of the two fracture types in our study, partly based on the high prevalence, partly on the fact that previous epidemiological studies had found varying results regarding risk factors for ankle fractures, and whether they are associated with osteoporosis or not. As discussed in Paper IV and section 1.6, some studies have been performed, but these are heterogenous and difficult to compare. Some of these studies conclude that low BMD is a risk factor for ankle fracture [187-189], others find no such correlation [190-193]. Being overweight or obese has been identified as a risk factor in several studies [75, 78, 79, 160, 187, 192, 194], most of these include postmenopausal and older women. Other risk factors discussed are age, sex, smoking, level of physical activity, previous fractures or falls, diabetes, polypharmacy, deteriorated bone architecture and trabecular bone score (TBS). In our study, we included 108 ankle fractures, with a mean age of 57.4 years, and 77% women. Older age gave lower odds of fracture. One possible explanation for this could be a lower degree of vigorous physical and sports activities with older age. However, the level of activity as assessed by the IPAQ did not significantly differ between the ankle fracture patients and controls without a fracture history. We might speculate that the elderly sustain different peripheral fractures in the case of a fall, because of different biomechanical factors at play. Daily use of three or more prescribed drugs gave an adjusted OR of 1.40 for ankle fracture, but the result was not significant. Male sex was a significant risk factor for ankle fracture, the opposite result as would be expected with an osteoporosis-related fracture type. The results from our study regarding risk factors for ankle fracture are summed up in *Figure 13*:

Variable	OR	95% CI
BMI*	1.391	1.086–1.792
Current smoker	1.724	0.835–3.558
Previous smoker	0.894	0.523–1.519
Osteoporosis	1.71	0.855–3.431
Osteopenia	1.29	0.733–2.273
Age >65	0.587	0.329–1.023
Male sex	2.199	1.238–3.915

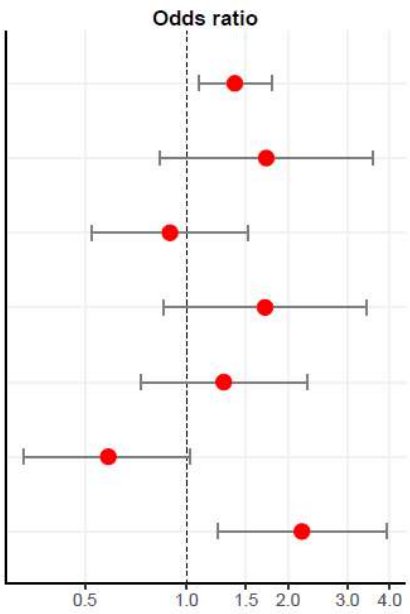


Figure 13: Risk factors for ankle fracture.

The figure shows multivariable odds ratios (ORs) with 95 % CIs for different risk factors comparing ankle fractures to controls, adjusted for all examined variables. * Per 5 BMI units. Whiskers represent 95 % confidence intervals.

5.4 Osteoporosis and the AO classification of distal radius fractures

In the osteoporosis outpatient clinic where the study was conducted, patients are referred to DXA scanning from both orthopedic surgeons and primary care physicians. Reading referrals, there seemed to us to be a clinical assumption that the more complex or severe the peripheral fracture, the higher the likelihood of osteoporosis. However, searching the literature for studies examining this topic, there were few to be found [195-199]. In our study, patients with osteoporosis did not have increased odds of a more complex distal radius fracture, defined as AO type B and C, versus type A (OR 1.11, 95 % CI 0.52-2.33), when compared to those with osteopenia or normal

BMD. Type B fractures had a higher mean BMD than type A and C (*Figure 14*), and also had a higher mean BMI. A higher percentage with type B fractures were male compared to type A and C.

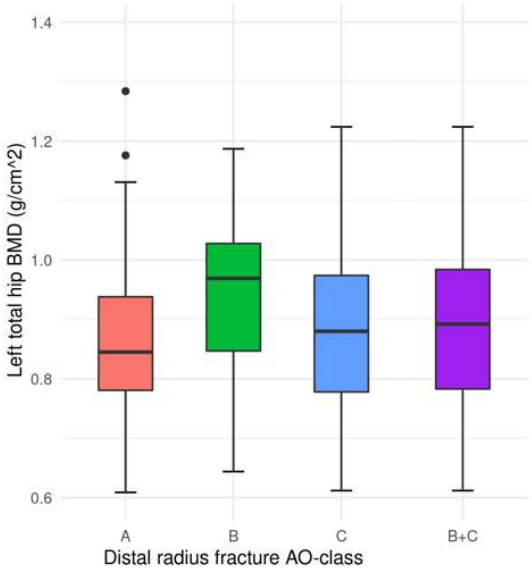


Figure 14: Box plot illustrating left hip BMD in different AO subgroups.

Centre horizontal line of the boxes represents the median. The boxes contain Q1 (25th Percentile) to Q3 (75th Percentile). IQR (Interquartile range) is the distance between Q1 and Q3. The bottom whiskers: less than Q1 – 1.5*IQR. The upper whiskers: greater than Q3 + 1.5*IQR.

Low energy trauma was associated with less complex fractures (type A). And, even though not statistically different, there is a trend towards a higher mean BMD in patients with distal radius fractures regarded as most severe (type C) compared to the less severe type A. A similar result was found in the study by Clayton et al [197]. As we stated in Paper III, the AO classification system does not fully capture the complexity and severity of distal radius fractures. Studies have found an association between low BMD and other radiographic deformities, such as ulnar variance, radial

inclination and dorsal angulation [200]. The thickness of cortical bone is greater in the metaphyseal area compared to the epiphyseal/intra-articular area. It may therefore be mechanically plausible that patients with osteoporosis, e.g. with reduced cortical thickness, would fracture easier in the methaphyseal area, and therefore suffer a type A fracture instead of a intraarticular type B or C fracture [198]. Xie et al [195] looked at the contralateral non-fractured radius in 70 women with recent distal radius fractures, and found that the mean cortical thickness was lower in displaced compared to non-displaced fractures, supporting this theory. Dhainut et al [199], assessing 110 female patients with fragility fractures of the distal radius, hypothesize that severity of such a fracture is more associated with bone quality parameters, rather than BMD. Their theory is supported by a study that found reduced bone material strength as measured by impact microindentation in patients with distal radius fractures compared to non-fracture controls [201]. Another interesting theory to consider is that people who have been diagnosed with osteoporosis may behave differently because of fear of falling and the awareness of an increased fracture risk, perhaps avoiding certain activities.

5.5 Overweight and the D-W classification of ankle fractures

Of the 108 patients with ankle fractures and available radiographic imaging, 17 patients had a type A fracture, 71 type B, and 20 a type C fracture according to the D-W classification system. There were clear differences in the prevalence of overweight and obesity between D-W subgroups, the most striking being 38.0 and 40.0 % of individuals with obesity in D-W type B and C, respectively, compared to 17.7 % in the patients with D-W type A fracture. The prevalence of overweight and obesity, as well as mean BMI, in ankle fracture patients, fracture subgroups and controls is illustrated in *Table 5*:

	n	Age mean (SD)	Women %	BMI (SD)	Over-weight * %	Obesity† %	Obesity + overweight %
Ankle fractures	108	57.4 (10.0)	77	28.7 (4.9)	38.0	35.2	73.2
D-W A	17	57.0 (9.1)	58	26.1 (4.2)	35.3	17.7	52.9
D-W B	71	57.2 (9.9)	74	28.8 (4.8)	36.6	38.0	74.7
D-W C	20	58.3 (11.5)	60	30.3 (5.5)	45.0	40.0	85.0
Controls	199	60.4 (10.5)	82	27.2 (5.2)	35.7	25.1	60.1

Table 5: Age, sex, and prevalence of overweight and obesity in ankle fractures, ankle fracture D-W subgroups and controls.

The median BMI in the type A group was 25.3, compared to 28.4 in the combined D-W type B or C fracture group, a result that was statistically significant. In Paper IV, we report that patients with overweight had a significantly higher odds of having a B or C fracture compared to type A. Considering that high body weight adds to the force in a fall or an ankle sprain, this does not come as a surprise. Even though the trauma mechanism was per definition a low energy trauma in approximately 70 % of cases, a high body weight increases the strain on the bone structures, and what seems like a small trauma, can lead to a serious injury. The fact that individuals with a high body weight seem to have a predisposition to fall sideways or backwards instead of forwards [202], may also be significant in the resulting fracture type. There are however, methodological issues that require mentioning, as are also briefly discussed in paper IV. We chose to combine the D-W types B and C into one group in our statistical analyses, since both these fracture subtypes are at risk of syndesmosis disruption, and subsequently, instability of the fracture [81]. The type B fracture is sometimes stable, sometimes unstable, and more diagnostic testing is often required to establish the need for surgical intervention. In order to assess the stability of the

syndesmosis and deltoid ligament, being essential for ankle joint stability, stress radiographs are recommended in addition to the clinical assessment by the orthopedic surgeon [203]. However, D-W type B and type C are known to differ in trauma mechanism, type B usually caused by a combination of supination and external rotation of the ankle joint, compared to type C more often caused by a pronation-abduction trauma [204]. These differences in trauma mechanisms are the basis of another classification system of ankle fractures, the Lauge-Hansen classification. Including this in our study might have added to the clinical relevance of our results. However, our results are in line with the study by King et al [205], increasing the probability that we have in fact been able to demonstrate a true association. Their study was a retrospective review of 280 patients with ankle fractures, using a multivariate cumulative logit model to assess the relationship between obesity and the D-W classification. They concluded that patients with a BMI of 30 kg/m^2 or greater had an OR of 1.78 of having a D-W C fracture compared to types A and B, and of D-W B and C, compared to type A. Other studies have found a higher mean BMI in patients with displaced ankle fractures compared to those with undisplaced fractures [206, 207], but these studies have not assessed the D-W classification.

5.6 Preventing fractures in clinical practice

Identification of subjects at high risk of fracture is fundamental if we are to improve our fracture preventing measures, and ensure that these are effective. As the population demographics changes, so must our strategies. Some of the changes having been discussed in this dissertation are: the aging population, and subsequently, the increased number of major osteoporotic fractures, the increasing number of patients being diagnosed with celiac disease in adulthood, and the obesity epidemic. But these factors are small pieces in a huge puzzle, and it may be argued that small pieces have little impact. They are however, all interconnected, as illustrated in *Figure 15*. And for each step on the path to a better understanding of interactions between different factors, the

better we will be able to tailor necessary population based strategies to prevent fractures.

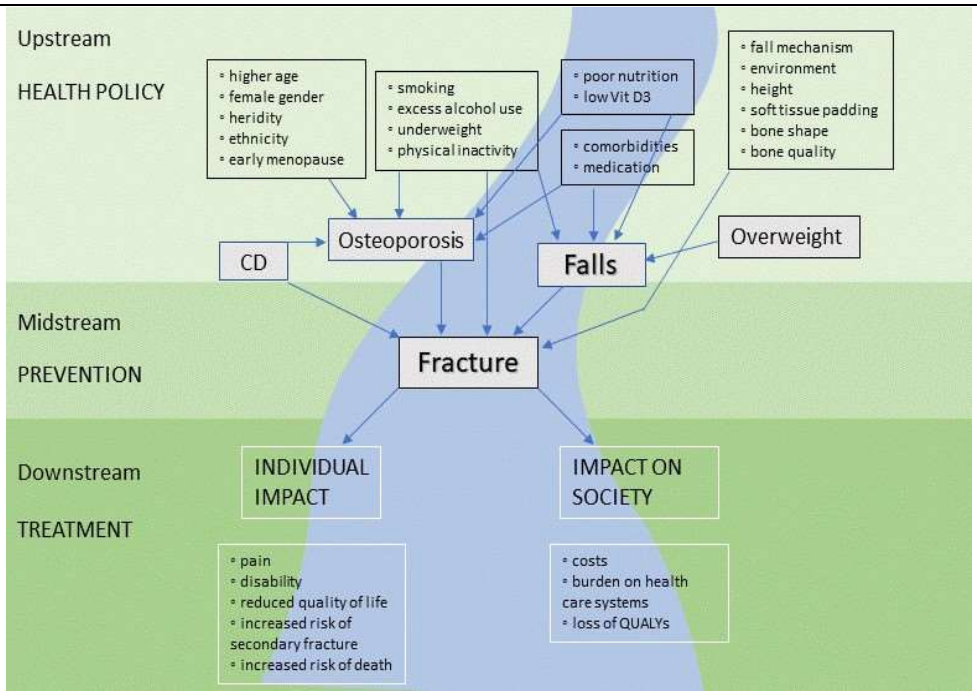


Figure 15: Wide perspective "upstream-downstream" illustration of fractures.

The factors primarily focused on in this thesis are in brackets.

6. METHODOLOGICAL CONSIDERATIONS

6.1 Study design

The results presented in this thesis are based upon a case-control study, designed as an epidemiological research project with the main goal to identify subgroups in populations being at high risk of fracture.

A case-control study is appropriate for investigating a suspected risk factor for a certain outcome, especially when the latency period between the exposure we want to examine (CD) and the possible outcome (fracture) is long. In the design phase of the study, we had the research question presented in Paper II as the main focus. Based on available literature, we assumed a prevalence of CD (by positive TG2 or known CD) to be 1 % in the general population, and 5 % in the fracture patient group. Our results, however, showed 1 % prevalence in the general population and 2.5 % in the fracture patient group. Thus, we recalculated the sample size and realized that we would need to enlarge the study to include 1000 controls and 2000 fracture patients. This was unfortunately not possible to achieve within the time limits of the PhD period, both in terms of financial reasons (PhD scholarship) and the estimated strain on the rheumatology outpatient clinic.

In papers III and IV, we described and compared the prevalence of clinical risk factors for the two included fracture types (the outcome variables for Paper III being distal radius fracture and the AO classification subgroup, ankle fracture and D-W classification subgroup in Paper IV). The epidemiology of ankle fractures and radius fracture differ. The most apparent difference found in our study was that distal radius fractures are strongly associated with osteoporosis, while ankle fractures are not. This may have diluted the results regarding increased fracture risk in CD addressed in Paper I, since the main reason for the increased fracture risk in CD is believed to be mediated through osteoporosis.

Since all the information was collected at the clinic visit, we were not able to study incidence, absolute risks or causality. As in all case-control studies, possible biases

must be carefully considered. This applies both to possible recall bias and selection bias (discussed in section 6.2.1).

6.2 Internal validity

The internal validity of a study is "the extent to which you can be confident that a cause-and-effect relationship established in a study cannot be explained by other factors" [208]. In order to ensure high internal validity, the three essential systematic errors (selection bias, information bias and confounding) must be considered.

6.2.1 Selection bias

Selection bias may occur at the time of recruitment of subjects. Selection errors can be related to the willingness of the patients and controls to participate. We invited patients and controls to participate in a study performing DXA scans. Patients with fracture, or controls, already having being diagnosed with osteoporosis, could have chosen not to participate in the study, thinking this would not be useful for them. This might have caused an underrepresentation of subjects with osteoporosis, and consequently, may have led to a possible underestimation of the difference in BMD between patients and controls. Following this line of thinking, a lower proportion of participants with osteoporosis discovered, might also have led to a lower number of CD cases identified. Since fracture patients were asked face to face if they wanted to participate in the study, while the controls were invited by letter only, this might have caused some selection bias. Another aspect to consider, is that those agreeing to participate might have thought that this would be relevant for them, e.g. because of close family members with osteoporosis or CD. We unfortunately do not have any information on the non-attendees, rendering the degree of this possible selection bias unknown.

When inviting population-based controls, there is a possibility that individuals with better health and with a high degree of health awareness are more likely to participate than people with poorer health and a more unfavorable lifestyle. Such individuals can often have a healthy life style and few comorbidities, making the control group less likely to have osteoporosis than the population in general. We did not compare patients

and controls regarding socioeconomic status (level of education, average income or the number receiving social benefits) or self-perceived health, which may act as surrogate markers for general health. For many of the participants, the visit to the hospital clinic demanded traveling as much as four hours by means of private or public transport, again favoring the more healthy individuals. We did, however, in order to diminish this possible selection bias, offer to cover travel expenses, also when transportation by taxi was needed.

6.2.2 Information bias

Information bias is "bias that arises from systematic differences in the collection, recall, recording or handling of information used in a study. Major types of information bias are misclassification bias, observer bias, recall bias and reporting bias" [209].

Data collected through the questionnaire at inclusion could be subject to recall bias, and subsequently both under- and over reporting. E.g., information on smoking, alcohol intake and the use of some on demand medication can be under-reported, while information of physical activity can be over-reported. There is, however, no reason to suspect that this possible under- or over reporting would differ between patients and controls in this study.

All BMD measurements were performed on the same GE Lunar DXA device by the same technician, using a standardized procedure. This should have reduced the risk of observational bias of BMD values. Regarding Papers III and IV, misclassification of the radiological images is another possible source of information bias. However, all interpretations were done by the same experienced radiologist, reducing inter-observer variability, and the intra-observer reliability of the classification systems have been shown to be satisfactory [210, 211].

The main sources of possible information bias in our study affect mainly Paper 2, and is concerning 1) the CD serum analyses and 2) the way we defined CD in our statistical models. As described in section 3.3.3, the TG2 analyses were performed by

three different laboratories using different methods, and there were small differences in sensitivity and cut-off levels between the different techniques used. In Paper 2, we defined a positive TG2 as a strong marker for likely CD. This is a sensitive and reliable test, as discussed in section 1.8, but the gold standard for diagnosing CD in adults is duodenal biopsy. The participants in the study having a positive TG2 were referred to the gastroenterological department for further examination, but this data were not included in the study.

6.2.3 Confounding

Confounding is "a distortion in the estimated measure of association that occurs when the primary exposure of interest is mixed up with another factor that is associated with the outcome" [212]. It is therefore important to be aware of the possible confounders, and statistically adjust for them to make sure your results show true associations. We have included potential confounding variables in the different analyses according to clinical risk factors addressed in previous studies, and according to our own clinical experience. In paper II and IV, we adjusted for age and sex. In Paper II we additionally tested adjustment for other possible confounders (BMI, Vitamin D and smoking), which did not significantly affect the results. In Paper III, we adjusted for age, sex, BMI, smoking, BMD and low energy trauma. None the less, we can not rule out that some data may have been insufficiently controlled for, and there may be residual confounding. We have analyzed some variables both as categorical (e.g. osteoporosis, osteopenia or normal BMD) and as continuous (e.g. BMD total hip), which did not lead to significantly different results.

6.3 Generalizability

The external validity or generalizability of a study is to what degree the results can be extrapolated to populations other than those under study. We aimed for the results to be generalizable to all the inhabitants of Sogn & Fjordane county 40 years and older, and as a consequence of the study's inclusion procedures, we think this has been achieved. Systematic studies on the prevalence of CD in Norway or different regions

within the country, has to our knowledge not been performed. We can therefore not know if our findings are generalizable to other parts of Norway or Norway as a whole.

BMD values have been shown to differ between regions in Norway [175]. There has been shown ethnic differences in risk of hip fracture in Norway, all immigrant groups having a lower risk of hip fracture compared to the Norwegian-born [213]. None of the study participants in the FABB-study had an immigrant background due to population structure. A study by Solbraa et al, found that the population in Sogn & Fjordane were significantly more physically active compared to the rest of Norway [214]. The same study also found a higher prevalence of overweight or obesity in Sogn & Fjordane county (52.7 % compared to 48.3 % in Norway as a whole). These studies may indicate that the population of Sogn & Fjordane county in some aspects differ from the general population in Norway, which may affect the generalizability of our results.

6.4 Strengths and limitations

The county of Sogn & Fjordane has a stable population with little migration. The controls were from the same geographic area as the patients and examined in the same period of time, strengthening the comparability between groups with regard to potential drift in DXA and laboratory analyses. We chose population-based controls in order to reduce the risk of sampling bias. A large number of variables were collected, and the information on potential confounding factors was extensive. The study included both men and women, with no upper age limit. Setting the cutoff as low as 40 years was done in order to capture potential secondary osteoporosis, as in e.g. CD, in an early phase. Inclusion and examination of patients was performed only at one study site, ensuring that the same procedures were followed. The fact that only two clinicians were directly involved in collecting and registering of all data should also strengthen data consistency. All participants had a 30-minute session with one of these two rheumatologist, the questionnaire was reviewed together with the patients in order to clarify any misinterpretations. All DXA scans were performed by the same technician on one single machine, and all the radiological interpretations were

performed by one experienced radiologist. An additional strength in Paper III, is the availability of a supplementary CT scan in 68 % of the distal radius fractures.

In addition to the possible selection- and information biases discussed in section 6.2.1 and 6.2.2, the main limitation in the study is the lack of statistical power. The study was too small and statistically underpowered to yield significant results in Paper II. Another factor that might have affected the results presented in Paper II, is the female predominance among participants. Women have a higher risk of fracture in general, however, studies suggest that men with CD may have a higher risk of fracture than women with CD [134, 215]. And, as there are relatively few male subjects in our study, this may have diluted a potential difference in fracture risk between the CD and the non-CD groups. Regarding Paper III and IV, the FABB-study was not primarily designed to investigate the associations between variables such as osteoporosis and overweight and the radiological classification systems of distal radius- and ankle fractures. The study is underpowered to conclude on some aspects since there are few cases of some fracture subtypes, and no formal power analyses were performed.

Another limitation is the use of radiological classification systems as a surrogate for clinical severity of a fracture, which is a far more complex entity, and the classification systems are not able to capture all the facets concerning the patients' post-fracture challenges and functional outcome. For Papers III (AO-classification of distal radius fractures) and IV (using the D-W classification of lateral malleolar fractures), we chose to combine the B and C fracture subgroups, making the assumption that these fracture subtypes were more complex and being more prone to instability and need of surgical intervention than the fractures in the Type A category. It may also be that the two fracture classification groups we combine (fractures Type B and C) differ both in the typical trauma mechanism responsible for the injury, and in the "typical" patient for the specific fracture (e.g., the distal radius AO Type B fracture being relatively more common in men, and less often resulting from a low energy trauma, compared to Types A and C).

7. CONCLUSIONS AND CLINICAL IMPLICATIONS

There is a positive association between CD and risk of fracture. In our study, fracture patients had an odds ratio of 2.5 for a positive IgA TG2 serology test, a sensitive marker for CD. Our results support recommended clinical practice in Norway to be aware of CD as a common cause of secondary osteoporosis and fracture, and examine patients with CD-serology tests if suspicion arises. This case finding strategy will lead to more CD diagnoses being made. Initiating treatment with gluten-free diet and considering the patient for osteoporosis assessment, can prevent fractures. The increased fracture risk in CD is, however, moderate, and does not warrant systematical screening for CD in all adult patients presenting with fracture.

We found that the prevalence of osteoporosis was significantly higher in the distal radius fracture group than in the healthy controls. This is in line with previous studies, and confirms the close association between osteoporosis and distal radius fractures in adults, and supports the current guidelines when it comes to assessment of osteoporosis in order to prevent the next fracture from occurring. However, osteoporosis did not significantly increase the odds of ankle fractures, and such a fracture, even if sustained through a low-energy trauma mechanism, does not automatically indicate the need for further osteoporosis assessment. Higher BMI and male sex were identified to significantly increase the odds of ankle fractures in adults.

In order to see if the subtype of distal radius or ankle fractures could add information as to which fracture patients were at greater risk of osteoporosis, we looked at the AO subtypes of distal radius fracture, and the D-W classification system of distal fibula fractures. The patients with osteoporosis did not have increased odds of a more complex distal radius fracture compared to patients with osteopenia or normal BMD. Therefore, the AO-classification of distal radius fractures cannot be used to decide which patients should, or should not, be referred to further osteoporosis assessment. The same result was found in the case of the D-W classification subtypes of ankle fractures. The major risk factor for instability of a sustained distal fibula fracture was overweight and obesity, explained by the increased force a higher body weight adds to

the trauma mechanism. Overweight is a risk factor for certain types of fractures. But preventing or treating osteoporosis in patients who are overweight will probably not prevent ankle fractures. Fighting the obesity epidemic in society is of greater importance, and, taking measures to prevent falls and traumas. We also believe that increased mobility, balance and muscle strength in persons who are overweight will decrease the probability of falls, and of ankle fracture.

This work has mainly had a clinical aim, wanting to contribute to better tailored fracture risk assessment. We have touched upon the decisions needing to be made by both orthopedic surgeons, gastroenterologists, rheumatologist, general practitioners, patients, and by policy makers. Categorical advice is essential for impact, but we should never lose sight of the personal clinical decision needing to be made together with the individual at risk.

8. FUTURE STUDIES

The use of BMD values as the sole determinant of bone strength is challenging. In the case of CD, an impairment in bone microarchitecture using TBS has been demonstrated (27, 28). We did not have this software available at the time of the inclusion of study participants, and larger studies looking at TBS and fracture risk in patients with CD would be useful. The same applies for patients with overweight and obesity, where the comparison to the reference population in the DXA machine, with a lower mean BMI, is a concern when it comes to validity. The additional estimation of total body fat mass and various body composition estimates as part of the DXA procedure could also be of interest when attempting to estimate bone health and fracture risk in this group of patients, and there is a need for further research in order to establish the optimal approach.

The use of both TBS, and perhaps also bone formation and reabsorption markers (such as P1NP and CTX) and OPG antibodies, could perhaps add to the predictive value of a bone health assessment. To our knowledge, studies looking at TBS scores and severity

of fractures have not been performed, and could also contribute with valuable insights regarding the epidemiology of fracture subtypes. In the distal radius fracture patients, it would be interesting to see if additional measurement of BMD in the distal radius by DXA could add to the risk assessment, both for risk of fracture, and to risk of specific fracture subtypes. A recent study performed additional DXA of the distal 1/3 of the radius on patients with celiac disease [216], and recommends adding this to the standard DXA analysis of lumbar spine and hips in patients with CD, in order to avoid underestimation of osteoporosis.

The effect of treatment with anti-resorptive medication for osteoporosis in patients with CD has not been systematically reviewed, and such studies would be useful for this large groups of patients. Previous small studies have indicated no differences between gluten-free diet alone and diet plus bisphosphonates (35, 36).

Findings from this thesis are not sufficient to establish if there truly is an association between osteoporosis and ankle fracture, and larger studies are needed in order to conclude on this research question.

APPENDICIES

1. Information poster

2. Information given to fracture patients

FORESPØRSEL OM Å DELTA I

FABB-STUDIEN:

Forekomst **A**v **B**enskjørhet og **B**lodprøvemarkør på cøliaki hos pasienter med underarms- og ankelbrudd i Sogn og Fjordane.

Du har fått påvist et brudd i underarm eller ankel. Slike brudd kan hos noen skyldes benskjørhet (osteoporose), og det er vist at spesielt underarmsbrudd kan være første tegn på denne tilstanden. Statens legemiddelverk og verdens helseorganisasjon (WHO) anbefaler at alle som har gjennomgått underarmsbrudd etter fylte 50 år utredes med bentetthetsmåling for å avsløre mulig underliggende osteoporose. Risiko for fremtidige brudd kan reduseres dersom benskjørhet diagnostiseres og behandles. Ved revmatologisk poliklinikk i Førde utreder vi personer med hensyn til benskjørhet og gir råd om behandling.

Cøliaki er en tynntarmssykdom der inntak av gluten gir betennelse i tynntarmsslimhinnen og gir økt risiko for nedsatt beintetthet. Hovedsymptomene er mageplager, jernmangel og trøtthet. Mange har derimot lite eller ingen plager. Det er likevel viktig å oppdage sykdommen, blant annet gir cøliaki en liten økning i risiko for enkelte typer kreft. Behandlingen er livslangt glutenfritt kosthold. Positiv blodprøve på et antistoff mot et enzym som omdanner gluten i tarmen, vevsglutaminase, gir sterk mistanke om denne tilstanden.

Vi ønsker å undersøke om pasienter i Sogn og Fjordane over 40 år med brudd i underarm eller ankel har benskjørhet som trenger behandling. Videre ønsker vi å se på hvor stor andel av de med brudd som har underliggende cølaki. Vi måler bentetthet på revmatologisk poliklinikk. Dette er en røntgenundersøkelse som er riskofri og tar ca 20 minutter. Samme dag vil det bli tatt blodprøver med tanke på påvisbare årsaker til benskjørhet, inkludert den nevnte prøven der utslag gir mistanke om cøliaki. Det vil også bli fryst ned en blodprøve til senere analyse av eventuelle nye markører som kan forklare årsak til osteoporose, cøliaki eller brudd. Dersom det senere blir aktuelt å bruke disse fryseprøvene til forskning, må det innhentes godkjennelse fra Regional Etisk Komite om dette. Du vil bli bedt om å svare på et spørreskjema om bl.a tidligere sykdommer, kosthold og medikamentbruk. Du vil også bli bedt om å underskrive en samtykkeerklæring slik at resultatene kan brukes i forskningen. Opplysningene som er registrert vil bli oppbevart i minimum 10 år. Alle opplysninger fra deg vil bli behandlet konfidensielt, og oppbevares i avidentifisert form. En kode knytter deg til dine opplysninger. Du kan når som helst be om å få innsyn i hva som er registrert om deg og trekke deg fra prosjektet om du vil det.

Ønsker du å delta i studien, vil behandlende lege i akuttmottak eller på ortopedisk poliklinikk henvise deg til oss. Det vil bli kostnad som vanlig egenandel, og du har rett til å få dekket reiseutgifter som ved en vanlig poliklinisk undersøkelse. Ønsker du ikke å delta i studien, men likevel få målt bentetthet, kan du be behandlende lege eller fastlegen din om henvising til revmatologisk poliklinikk etter vanlige retningslinjer.

Dersom du skulle få påvist benskjørhet vil vi tilby etablert behandling for å kunne forebygge nye brudd i fremtiden. Dersom det er utslag på blodprøven som gir mistanke om cøliaki, anbefaler vi at vi får henvise deg videre til medisinsk poliklinikk for gastroskopi. Det er en kikkertundersøkelse av magesekken der en kan ta en liten prøve av tolvfingertarmen for å bekrefte eller avkrefte mistanken om foreligger cøliaki. Dette er imidlertid ikke et krav, men noe som vil bli diskutert med deg.

Vi håper du kan tenke deg å delta i vår studie, og ser frem til å møte deg på revmatologisk poliklinikk. Dersom du er i tvil på om du ønsker å delta i studien er du velkommen til å ta kontakt med revmatologisk poliklinikk på telefon 57839381 og be om å få snakke med dr Hjelle eller dr Mielnik for ytterligere informasjon.

Med vennlig hilsen

Anja Myhre Hjelle

Konstituert overlege Revmatologisk avdeling

Førde Sentralsykehus

3. Information given to controls

FORESPØRSEL OM Å DELTA I

FABB-STUDIEN:

Forekomst **a**v **b**enskjørhet og **b**lodprøvemarkør på cøliaki hos pasienter med underarms- og ankelbrudd i Sogn og Fjordane.

Vi skal i denne studien undersøke om pasienter med brudd har større risiko for benskjørhet (osteoporose) og cøliaki. I den forbindelse trenger vi friske kontroller å sammenligne med. Du har blitt utvalgt tilfeldig gjennom Statistisk Sentralbyrå, og inviteres dermed til å delta i studien. Det er mange som har osteoporose som ennå ikke har hatt brudd, og risiko for fremtidige brudd kan reduseres dersom benskjørhet diagnostiseres og behandles. Ved revmatologisk poliklinikk i Førde utreder vi personer med hensyn til benskjørhet og gir råd om behandling.

Dersom du har hatt brudd i armer, bein (brudd i fingre og tær er ingen hindring) eller rygg kan du ikke delta i studien. Øvrige sykdommer du eventuelt har er ingen hindring for deltakelse, heller ikke kjent cøliaki eller benskjørhet.

Cøliaki er en tynntarmssykdom der inntak av gluten gir betennelse i tynntarmsslimhinnen og gir økt risiko for benskjørhet. Hovedsymptomene er mageplager, jernmangel og trøtthet. Mange har derimot lite eller ingen plager. Det er likevel viktig å oppdage sykdommen, blant annet gir cøliaki en liten økning i risiko for enkelte typer kreft. Behandlingen er livslangt glutenfritt kosthold. Positiv blodprøve på et antistoff mot et enzym som omdanner gluten i tarmen gir sterk mistanke om denne tilstanden.

Vi inviterer deg til å få utført bentetthetsmåling på revmatologisk poliklinikk i Førde. Dette er en røntgenundersøkelse som er risikofri og tar ca 20 minutter. Samme dag vil det bli tatt blodprøver med tanke på påvisbare årsaker til benskjørhet. Det vil også bli fryst ned en blodprøve til senere analyse av eventuelle nye markører som kan forklare årsak til osteoporose, cøliaki eller brudd. Dersom det senere blir aktuelt å bruke disse fryseprøvene til forskning, må det innhentes godkjennelse fra Regional Etisk Komite om dette. Du vil bli bedt om å svare på et spørreskjema om blant annet tidligere sykdommer, kosthold og medikamentbruk. Du vil også bli bedt om å underskrive en samtykkeerklæring slik at resultatene kan brukes i forskningen. Opplysningene som er registrert vil bli oppbevart i minimum 10 år. Alle opplysninger fra deg vil bli behandlet konfidensielt, og oppbevares i avidentifisert form. En kode knytter deg til dine opplysninger. Du kan når som helst be om å få innsyn i hva som er registrert om deg og trekke deg fra studien om du vil det.

Ønsker du å delta i studien ber vi deg returnere svarslippen på neste side. Du har rett til å få dekket reiseutgifter, og det vil ikke bli kostnader for deg ved selve undersøkelsen. Vi kan ikke dekke tapt arbeidsfortjeneste for undersøkelsesdagen.

Dersom du skulle få påvist benskjørhet vil vi tilby etablert behandling for å kunne forebygge brudd i fremtiden. Dersom det er utslag på blodprøven som gir mistanke om cøliaki, anbefaler vi at vi får henvise deg videre til medisinsk poliklinikk for gastroskopi. Det er en kikkertundersøkelse av magesekken der en kan ta en liten prøve av tolvfingertarmen for å bekrefte eller avkrefte mistanken om cøliaki. Dette er imidlertid ikke et krav.

Vi håper du kan tenke deg å delta i vår studie, og ser frem til å møte deg på revmatologisk poliklinikk. Dersom du er i tvil på om du ønsker å delta i studien er du velkommen til å ta kontakt med revmatologisk poliklinikk på telefon 578 39381 og be om å få snakke med dr Hjelle eller dr Mielnik for ytterligere informasjon.

Med vennlig hilsen

Anja Myhre Hjelle

Konstituert overlege Revmatologisk avdeling

Førde Sentralsykehus

Ja, jeg ønsker å delta i studien. Jeg mottar dermed innkalling til undersøkelse i posten, og får samtidig spørreskjema og samtykkeskjema til utfylling.

Sted: _____

Dato: _____

Navn (blokkbokstaver): _____

Signatur: _____

_____

Sendes i vedlagt frankert konvolutt.

FABB-studien Helse Førde

4. Consent form

SAMTYKKESKJEMA FOR DELTAKELSE I

FABB-STUDIEN:

Forekomst av benskjørhet og blodprøvemarkør på cøliaki hos pasienter med underarms- og ankelbrudd i Sogn og Fjordane.

Prosjektleder: Pawel Mielnik

Forskningsmedarbeier: Anja Myhre Hjelle

Prosjektnummer: 970114

Viser til utdelt informasjonsskriv angående studiens bakgrunn, hensikt og gjennomførelse.

Hva skjer med prøvene og informasjonen om deg?

Det er frivillig å delta i studien. Om du nå sier ja til å delta, kan du senere når som helst og uten å oppgi noen grunn, trekke tilbake ditt samtykke. Prøvene og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Opplysningene som er registrert vil bli oppbevart i minimum 10 år. Alle opplysninger fra deg vil bli behandlet konfidensielt, og oppbevares i avidentifisert form. En kode knytter deg til dine opplysninger. Det er kun autorisert personell knyttet til prosjektet som har adgang til opplysningene.

Informasjon om dine rettigheter

a) Personvern

Opplysninger som registreres om deg er resultat på bentetthetsmåling, blodprøvesvar og svar som er angitt på spørreskjemaet. De konfidensielle data er lagret på Helse Førdes forskningssverver. Databehandlingsansvalig er Helse Vest IKT.

b) Biobank

En del av blodprøven som tas undersøkelsesdagen vil bli lagret i en forskningsbiobank ved Førde sykehus. Dette med tanke på å senere kunne undersøke blodet med tanke på nye faktorer i mekanismene bak osteoporose og/eller cøliaki, inkludert genetiske faktorer. Dersom du sier ja til å delta i studien, gir du også samtykke til dette. Biobanken planlegges å vare i minimum 10 år. Etter avsluttet periode vil materiale og opplysninger bli ødelagt etter interne retningslinjer.

c) Utlevering av materiale og opplysninger til andre

Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger utleveres til samarbeidende forskere i Helse Vest.

d) Rett til innsyn og sletting av opplysninger om deg og sletting av prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

e) Økonomi og rolle

Pasienter med brudd betaler etter henvisning til bentetthetsmåling vanlig egenandel for undersøkelse og legekonsultasjon ved revmatologisk poliklinikk. Kontroller uten brudd blir undersøkt uten kostnad, men ved evt oppfølging etter positive funn vil det bli krevd egenadel etter vanlige retningslinjer. Prosjektet fikk tildelt forskningsmidler fra Helse Førde i 2011.

f) Forsikring

Personer som deltar i studien er dekket av pasientskadeerstatningsordninger ved eventuelle uhell eller komplikasjoner.

Samtykke til deltakelse

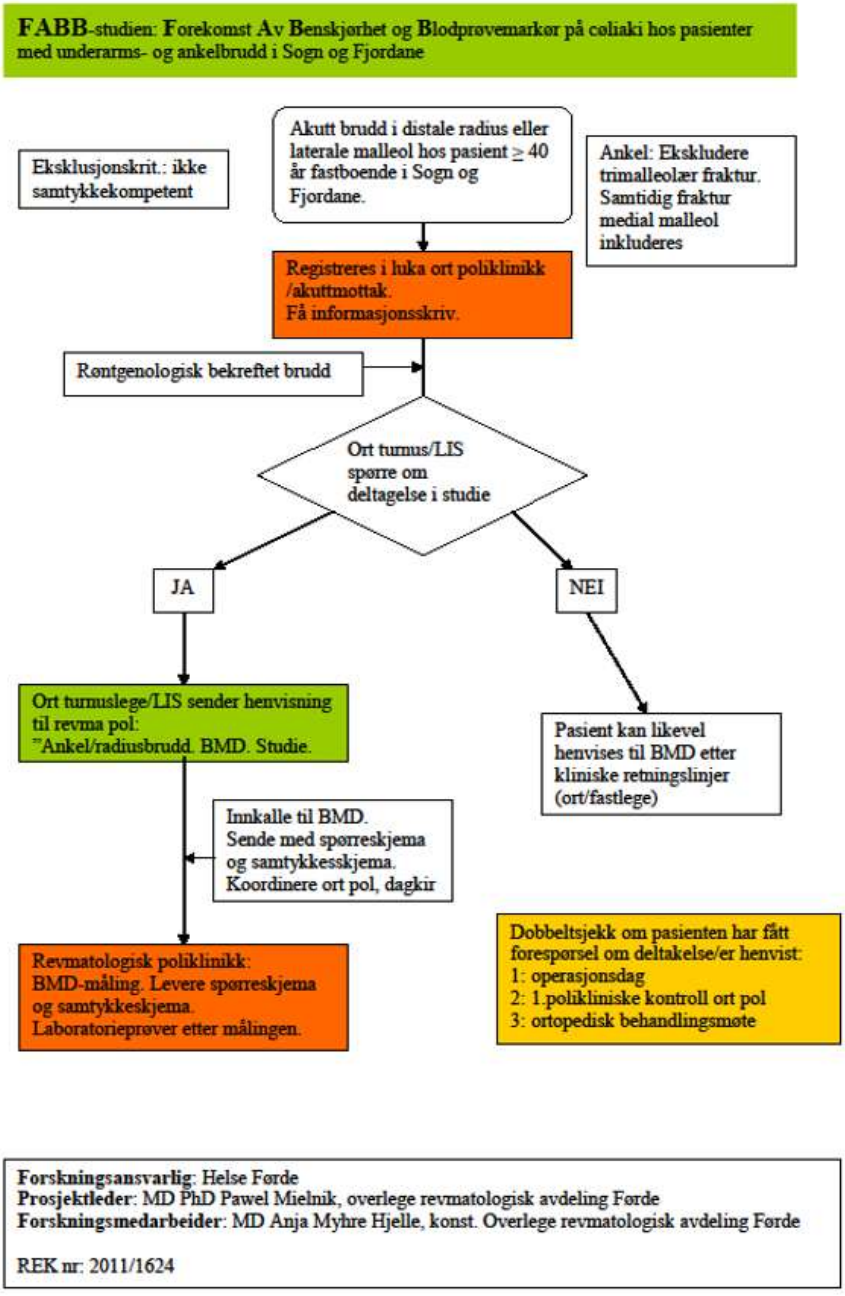
Jeg er villig til å delta i studien. Signatur prosjektmedarbeider

Sted: _____

Dato: _____ Dato: _____

Signatur: _____ Signatur: _____

5. Flow chart for the orthopedic department



Forskningsansvarlig: Helse Førde
Prosjektleder: MD PhD Pawel Mielnik, overlege revmatologisk avdeling Førde
Forskningsmedarbeider: MD Anja Myhre Hjelle, konst. Overlege revmatologisk avdeling Førde

REK nr: 2011/1624

6. Questionnaire

Forskningsnr:

SPØRRESKJEMA TIL DELTAGERE I

FABB-studien

Forekomst **A**v **B**enskjørhet og **B**lodprøvemarkør på cøliaki hos pasienter med underarms- og ankelbrudd i Sogn og Fjordane.

Sett kryss i ruten som svar. Ved feil og du har behov for å rette, fyll ut feil valgt rute slik: ■, og sett dine initialer bak rettelsen. Signer etter fullført skjema med initialer og dato, ikke med fullt navn.

1) Arv

a) Har din mor hatt brudd etter overgangsalderen? Ja Nei Vet ikke

b) Har din far hatt brudd etter 40-årsalderen? Ja Nei Vet ikke

c) Hvor mange søsken har du? *Antall:*____

d) Har en eller flere av dine søsken hatt brudd etter 40-årsalderen? Ja Nei Vet ikke

e) Har du cøliaki? Ja Nei Vet ikke

f) Kjenner du til 1.gradsslektninger (forelder, søsken eller barn) har cøliaki? Ja Nei Vet ikke

2) Spørsmål om kost og ernæringsstatus

a) Hvor mye melk drikker du?

> 0,5 liter daglig daglig < 0,5 liter sjeldent eller aldri

b) Hvor ofte spiser du hvitost (antall høvlede osteskiver):

mer enn 3 skiver daglig mindre enn 3 skiver daglig aldri

c) Tar du vitamintilskudd? Ja Nei Vet ikke

d) Tar du kalk? Ja Nei Vet ikke

e) Tar du D-vitaminer? Ja Nei Vet ikke

f) Tar du tilskudd av omega3/tran/selolje? Ja Nei Vet ikke

g) Hva er din nåværende høyde? _____ meter

h) Hva var din høyeste målte høyde? _____ meter

i) Hva veier du? _____ kg

3) For deg som har hatt nylig brudd: Skademekanisme

Hvordan skjedde bruddet?

Lavenergibrudd (energi tilsvarende fall fra egen høyde eller lavere, evt uten skade)

Høyenergibrudd (mer kraft i skademekanismen enn som definert over)

Skadested utendørs

Fall på snø/is

Hvilken måned skjedde skaden i? _____

4) Spørsmål om tidligere brudd

a) har du hatt brudd tidligere? Ja Nei

i) hvor? _____

ii) i hvilken alder? _____

5) Spørsmål om fysisk aktivitet

Meget anstrengende aktivitet er aktivitet som krever hard innsats og som får deg til å puste mye mer enn vanlig. Ta bare med aktiviteter som varer minst 10 minutter i strekk.

a) Hvor mange dager i løpet av de siste 7 dagene har du drevet med meget anstrengende fysisk aktivitet som tunge løft, gravearbeid, aerobics, løp eller rask sykling?

_____ **dager** ingen meget anstrengende aktivitet → gå rett til spørsmål c)

b) Hvor lang tid brukte du vanligvis på meget anstrengende fysisk aktivitet på en av disse dagene?

_____ **timer per dag** _____ **minutter per dag** vet ikke/usikker

Middels anstrengende aktivitet er aktivitet som krever moderat innsats og får deg til å puste litt mer enn vanlig. Ta bare med aktiviteter som varer i minst 10 minutter i strekk.

c) Hvor mange dager i løpet av de siste 7 dagene har du drevet med middels anstrengende fysisk aktivitet som å bære lette ting, jogge eller sykle i moderat tempo? Ikke ta med gange.

_____ **dager** ingen middels anstrengende aktivitet → gå rett til spørsmål e)

d) Hvor lang tid brukte du vanligvis på middels anstrengende fysisk aktivitet på en av disse dagene?

_____ **timer per dag** _____ **minutter per dag** vet ikke/usikker

Tenk på tiden du har brukt på å gå de siste 7 dagene. Dette inkluderer gange på jobb og hjemme, gange fra er sted til et annet eller gange som du gjør på tur eller som trening på fritiden.

e) Hvor mange dager i løpet av de siste 7 dagene gikk du i minst 10 minutter i strekk?

_____ **dager** gikk ikke → gå rett til spørsmål g)

f) Hvor lang tid brukte du vanligvis på å gå på en av disse dagene?

_____ **timer per dag** _____ **minutter per dag** vet ikke/usikker

Det neste spørsmålet omhandler sitting. Inkluder tid du har brukt på å sitte på jobb, hjemme, på kurs og på fritiden. Dette kan tilsvare tiden du sitter ved et arbeidsbord, hos venner, mens du leser, eller sitter eller ligger for å se på TV.

g) Hvor lang tid brukte du på å sitte på en vanlig hverdag i løpet av de siste 7 dagene?

_____ **timer per dag** _____ **minutter per dag** vet ikke/usikker

h) Tenk tilbake i tid. Hvor ofte drev du med fysisk aktivitet eller idrett så mye at du ble andpusten og/eller svett da du var:
Sett ett kryss for hver aldersgruppe

	Under 10 år	10-14 år	15-20 år	20-30 år
Aldri				
Mindre enn en gang/måned				
1-3 ganger/måned				
1 gang/uke				
2-3 ganger/uke				
4-6 ganger/uke				
Hver dag				

6) Spørsmål om hormoner (besvares kun av kvinner)

a) Hvor gammel var du da du fikk din første menstruasjon? _____ år

b) Har du hatt regelmessig menstruasjon? Ja Nei

c) Har du gjennomgått underlivsoperasjon? Ja Nei

i) i hvilken alder? _____ år

ii) ble eggstokkene fjernet? Ja Nei Vet ikke

d) Har du passert overgangsalderen? Ja Nei Vet ikke

i) ved hvilken alder? _____ år

e) Har du fått hormonbehandling i forbindelse med overgangsalderen?
Ja Nei Vet ikke

i) hvilket årstall fikk du hormonbehandling? _____
ii) var det stikkpiller/krem tablett plaster
iii) får du fortsatt hormoner? Ja Nei
iv) hvilken hormonbehandling får du (navn på medikament)? _____

7) Spørsmål om annen sykdom

Angi hvilke av sykdommene nedenfor du har, og ved hvilken alder du fikk diagnosen:

Sukkersyke/diabetes _____ år

Stoffskiftesykdom _____ år

Leddgikt _____ år

Crohns sykdom _____ år

Ulcerøs colitt _____ år

Astma eller KOLS _____ år

Epilepsi _____ år

Andre sykdommer? Hvilke? _____ ____ år

_____ ____ år

_____ ____ år

_____ ____ år

Til kvinner: Har du spontanabortert?

ja nei vet ikke

Hvis JA, antall ganger _____

Til menn: Har din partner noen gang spontanabortert?

ja nei vet ikke

Hvis JA, antall ganger _____

Bruker du glutenfri diett?

ja nei vet ikke

Har du fått stilt diagnosen Dermatitis Herpetiformis?

ja nei vet ikke

Har du fått stilt diagnosen cøliaki på bakgrunn av en vevsprøve fra tynntarmen tatt under en undersøkelse der du svelget en slange (gastroskopi?)

ja nei vet ikke

8) Bruk av medikamenter

Angi navnet på medikamenter som du nå bruker daglig.

Har du noen gang brukt Prednisolon tabletter i mer enn 3 måneder sammenhengende?

Ja Nei Vet ikke

9) Spørsmål om røyk og alkohol

a) Omtrent hvor ofte har du i løpet av det siste året drukket alkohol?

Lettøl og alkoholfritt øl regnes ikke med.

4-7 ganger i uka

2-3 ganger i uka

Ca 1 gang i uka

2-3 ganger per måned

Omtrent 1 gang per måned

Noen få ganger siste år

Har ikke drukket alkohol det siste året

Har aldri drukket alkohol

b) Når du har drukket alkohol, hvor mange glass/drinker har du vanligvis drukket?
_____ *antall*

c) Omtrent hvor mange ganger i løpet av det siste året har du drukket så mye som minst 5 glass og/eller drinker i løpet av ett døgn?
_____ *antall ganger*

d) Når du drikker alkohol, drikker du da vanligvis:
Øl

Vin

Brennevin

e) Har du røykt/røyker du daglig?
ja, nå

ja, tidligere

aldri

f) Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?
_____ år

g) Hvis du røyker daglig nå eller har røykt tidligere:

I: hvor mange sigaretter røyker/røykte du vanligvis daglig?

_____ *antall sigaretter*

II: hvor gammel var du da du begynte å røyke daglig?

_____ år

III: hvor mange år til sammen har du røykt daglig?

_____ år

10) Spørsmål om mage/tarm funksjon

a) I hvilken grad har du hatt følgende plager de siste 12 måneder?

Kvalme	aldri	litt	mye
Halsbrann/sure oppstøt	aldri	litt	mye
Diare	aldri	litt	mye
Treg mage	aldri	litt	mye
Vekslende treg mage og diare	aldri	litt	mye
Oppblåsthet	aldri	litt	mye
Smerter i magen	aldri	litt	mye

b) Hvis du har hatt smerter i eller ubehag fra magen det siste året:

Er disse lokalisert øverst i magen? ja nei

Har du hatt plagene så ofte som 1 dag i uka eller mer de siste 3 mnd? ja nei

Blir plagene bedre etter avføring? ja nei

Har plagene sammenheng med hyppigere eller sjeldnere avføring enn vanlig?

ja nei

Har plagene noen sammenheng med løsere eller fastere avføring enn vanlig?

ja nei

Kommer plagene etter måltid? ja nei

Dato for utfylling: _____

Dine initialer: _____

Tilleggsinformasjon til Spørreskjema

Angående spørsmål 5 Fysisk aktivitet

Her ber vi deg svare på spørsmål om fysisk aktivitet i uken før det aktuelle bruddet, altså de 7 dagene før bruddet skjedde.

Mvh

Anja Myhre Hjelle og Pawel Mielnik

FABB-studien

Revmatologisk poliklinikk, Førde

7. REK approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Øyvind Straume	55978497	29.09.2011	2011/1624/REK vest
			Deres dato:	Deres referanse:
			23.08.2011	

Vår referanse må oppgis ved alle henvendelser

Pavel Mielnik
Helse Førde
6807 Førde

2011/1624 Forekomst av benskjørhet og blodprøvemarkør på coliaki hos pasienter med underarms- og ankelbrudd i Sogn og Fjordane.

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk i møtet 15.09.2011.

Prosjektomtale (revidert av REK):
Coliaki medfører økt risiko for osteoporose og de har redusert beintetthet (BMD). Noen studier viser at coliaki gir økt risiko for arm- og benbrudd, men forskningsresultatene her er ikke entydige og en mangler også gode studier på dette. Denne studien har som hensikt å se på om coliaki er en uavhengig risikofaktor for brudd, om pasienter med coliaki har lavere beintetthet en friske, en vil se på forekomst av osteoporose hos bruddpasienter og en vil undersøke bentetthet hos friske personer. I denne studien skal en inkludere pasienter 40 år og eldre med akutt underarmsbrudd og ankelbrudd. En vil også inkludere en kontrollgruppe bestående av friske alders- og kjønnsmatchede personer. Deltakelse i studien innebærer at det tas beintetthetsmåling, IgA antistoff vil bli målt, det vil bli foretatt blodprøveutredning, og spørreskjema skal fylles ut. Det opplyses om at det er ønskelig å ha fryseprøver for senere målinger av nye markører, inkludert genetiske, med tanke på risiko for utvikling av osteoporose, osteoporotiske brudd og/eller coliaki. En vil inkludere 600 deltakere i studien fordelt på 400 pasienter og 200 kontroller.

Forskningsetisk vurdering
REK Vest anser Helse Førde HF som forskningsansvarlig for denne studien.

Generelt:
Komiteen mener dette er en studie med et godt design som metodisk sett er lagt hensiktsmessig opp. Studie er stor og den har et potensiale for å komme deltakerne til gode. REK Vest har merket seg at en ønsker å ha fryseprøver for senere eventuelle målinger av nye markører, inkludert genetiske. Dette innebærer opprettelse av forskningsbiobank, noe som også søknaden omfatter.

Komiteen har ingen innvendinger til design eller metode.

Rekruttering/samtykke:
Informasjonsskrivene er av god kvalitet. Det går frem av skrivet at en ønsker å lagre biologisk materiale (blodprøve) for senere studier. I tilknytning til dette må det også skrives at dersom det er aktuelt å bruke materialet i senere forskning, skal en søke REK om godkjenning for dette. I skrivet til kontrollgruppen bør en si litt mer om hvordan en har funnet frem til disse og hvorfor de blir spurt om å delta. REK Vi har merket

Besøksadresse:
Haukeland Universitetssykehus,
Sentralblokken, 2. etg, Rom 4617

Telefon: 55975000
E-post: rek-vest@uib.no
Web:
http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK vest og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK vest, not to individual staff

oss at samtykkeerklæringen inneholder alternativ for stedfortredende samtykke. REK Vest ser ingen grunn til å inkludere personer som selv ikke er i stand til å avgi samtykke og vi forutsetter derfor at dette alternativet går ut.

Vedtak
Prosjektet godkjennes på betingelse av at ovennevnte vilkår tas til følge.

Godkjenningen av prosjektet gjelder til 31.05.2018. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.05.2023. Opplysningene skal deretter slettes eller anonymiseres, senest innen 30.11.2023.

Prosjektet skal sende sluttmelding til REK vest på fastsatt skjema senest 30.11.2018.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK. Vi gjør oppmerksom på at hvis endringene er "vesentlige", må prosjektleder sende ny søknad, eller REK kan pålegge at det sendes ny søknad.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jfr. helseforskningsloven § 10, 3 ledd og forvaltningsloven § 28. En eventuell klage sendes til REK vest. Klagefristen er tre uker fra mottak av dette brevet, jfr. forvaltningsloven § 29.

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen,

Jon Lekven (sign.)
dr.med./komiteleder

Arne Salbu
rådgiver

Kopi til: postmottak@helse-forde.no

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

No association between osteoporosis and AO classification of distal radius fractures: an observational study of 289 patients

Anja M. Hjelle[1,2,3*], Jan-Erik Gjertsen[4,5], Ellen M. Apalset[6,3], Roy M. Nilsen[7], Anja Lober[2], Grethe S. Tell[3] and Pawel Mielnik[1]

Abstract

Background: It is mechanically plausible that osteoporosis leads to more severe peripheral fractures, but studies investigating associations between BMD and radiographically verified complexity of distal radius fractures are scarce. This study aims to study the association between osteoporosis, as well as other risk factors for fracture, and the AO classification of distal radius fractures.

Methods: In this observational study, 289 consecutive patients aged ≥40 years with a distal radius fracture were included. Bone mineral density (BMD) of the hips and spine was measured by dual-energy x-ray absorptiometry (DXA), and comorbidities, medication, physical activity, smoking habits, body mass index (BMI), and history of previous fracture were registered. The distal radius fractures were classified according to the Müller AO system (AO) (type B and C regarded as most complex).

Results: Patients with osteoporosis ($n = 130$) did not have increased odds of a more complex distal radius fracture (type B + C, $n = 192$)) (n = vs type A ($n = 92$) (OR 1.1 [95% CI 0.5 to 2.3]) compared to those with osteopenia /normal BMD ($n = 159$). Patients with AO fracture types A or C had a higher prevalence of osteoporosis than patients with type B fracture.

Conclusions: Distal radius fracture patients with osteoporosis did not sustain more complex fractures than those with osteopenia/normal BMD according to the AO classification system. The AO classification of distal radius fracture cannot be used to decide which patients should be referred to DXA scan and considered for secondary fracture prevention.

Keywords: Osteoporosis, Dual energy x-ray absorptiometry, Distal radius fracture, AO classification

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Background

Distal radius fractures are the most common of all fractures during a lifespan. A Norwegian study found an overall annual incidence of 19.7 per 10,000 inhabitants 16 years or older [1]. In women, the incidence of distal radius fractures increases progressively with age from the perimenopausal period, while in men, the incidence remains low until later in life [2, 3]. According to the Swedish fracture registry (www.frakturregistret.se), 19, 357 women over the age of 60 suffered a distal radius fracture in 2018. Distal radius fractures are closely related to low bone mineral density (BMD) [4], and risk factors for fracture also include increasing age, female sex, low body mass index (BMI), smoking, postmenopausal status, low intake of dairy products, vitamin D deficiency, and autoimmune comorbidities. Patients sustaining a distal radius fracture have an increased risk of a major osteoporotic fracture (MOF) of the hip and vertebrae later in life [5, 6]. According to guidelines of fracture liaison services, a low energy fracture in an at-risk patient (e.g. > 50 years old) should lead to further examination with dual-energy x-ray absorptiometry (DXA) and treatment with anti-osteoporotic drugs if indicated [7].

When it comes to distal radius fractures and radiographic severity a few studies have been performed [8–12], but the number of patients examined are limited, the methods used differ, and conclusions are not easily drawn. Therefore, our aim was to further investigate if there is an association between osteoporosis and other well-known risk factors for osteoporotic fractures and AO classification of distal radius fractures.

Methods

Subjects

From March 1, 2012 until January 13, 2017, patients aged ≥40 years presenting with acute distal radius fracture at the Department of Orthopedic Surgery at District General Hospital of Førde (Sogn og Fjordane County) were included in a case control study. The study was primarily designed to explore the prevalence of celiac disease in patients with peripheral fractures compared to community-based controls. The original study has previously been described [13]. Fracture patients who fulfilled the inclusion criteria and consented to participate were referred for DXA scan and consideration of secondary fracture prevention ($n = 516$). Two hundred eighty-nine patients agreed to participate, giving an inclusion rate of 56%. We included both patients with low energy fractures (equivalent to fall from standing height or lower) and fractures due to traumas with higher energy. Five patients suffered multiple simultaneous fractures (one with bilateral radius fractures, one with an additional humerus fracture, one with an additional ankle fracture, and two with additional vertebral compression fractures).

Procedures and measurements

The radiographic distal radius series comprised standard anteroposterior and lateral radiographs. In 68% of cases (197 of 289 patients) a supplementary CT scan was available. The same radiologist classified the fractures as extra articular (type A), partly articular (type B) or complete articular (type C) according to the Müller AO-system (AO) [14, 15]. Types B and C were considered more complex than type A. In addition, the multifragmentary fractures (types A3, C2 and C3) combined were compared to the other AO fracture types. Five of the distal radius fractures could not be classified because the radiographic images had been performed elsewhere.

The BMD measurements were performed by DXA technology (Lunar Prodigy Rtg 5603, manufacture year 2000, GE Healthcare), with a daily quality assurance of +/− 2%. BMD was reported as g/cm^2 and T-scores by standard definition. Osteoporosis is defined as T-score ≤ − 2.5 in the femoral neck, total hip or lumbar spine. Osteopenia (low bone mineral density) is defined as T-score between − 1.0 and − 2.5 [16]. History of previous fractures, comorbidities, medications, and lifestyle factors were registered. The original documents from the orthopedic surgeons and examining rheumatologist were reviewed to classify the injury as due to a low energy trauma or not. Height and weight were measured as part of the DXA procedure. BMI was calculated and categorized into underweight (BMI < 18.5), normal weight (BMI 18.5–24.99), overweight (BMI 25–29.99) and obesity (BMI ≥ 30). Blood tests were analyzed to detect common causes of secondary osteoporosis [13].

Statistical analyses

We performed descriptive statistics for age, sex, BMI, number of patients with osteoporosis, osteopenia, and overweight in the distal radius fracture subgroups. Data between subgroups were compared using chi square or Fisher's exact test for categorical data and two-sample t-test or Mann-Whitney U test for continuous data. To assess risk factors associated with the complexity of fractures, we estimated odds ratios (ORs) with 95% confidence intervals (CIs) using unconditional logistic regression models. Complexity of fractures was defined as more radiological complex fractures (AO type B + C) as opposed to less complex fractures (AO type A). Relevant risk factors for complexity of fracture included osteoporosis, osteopenia, age > 65 years, male sex, BMI, and current and previous smoking. In all analyses, the association between the risk factor and the complexity of fractures was first examined crudely and then with adjustment for the other risk factors under study. All *p*-

values were two-sided and values below 0.05 were considered statistically significant. All calculations were performed using R version 3.6.2 (team).

Results

We found that 45.0% ($n = 130$) of patients with distal radius fracture had osteoporosis and 33% ($n = 95$) had osteopenia (Table 1). Patients with an AO type B fracture were younger, had a higher mean BMI, and the percentage of men was higher than in the groups with A or C fractures (Table 1). 29.4% of patients with type B fracture had osteoporosis compared to 46.7% of type A and 48.1% of type C (Table 1, Fig. 1). The patients with osteoporosis differed from the patients with osteopenia/normal BMD at a group level by having a statistically lower BMI (BMI 26 vs 27, p-value 0.005), being older (mean age 64 vs 53 years, p-value 0.01), a greater percentage were female (88% vs 75%, p-value 0.01), and there was a higher prevalence of current smoking (18% vs 13%, p-value 0.1). There was a significantly higher proportion with low energy trauma mechanism in the patients with radius fracture and osteoporosis compared to those with radius fractures and normal BMD/osteopenia (77% vs 57%, p-value < 0.001).

The OR of sustaining a distal radius fracture type B or C vs. A was not significantly affected by the presence of osteoporosis (Table 2). Current smoking and low energy trauma injury were associated with less complex fractures (Table 2). When combining the multifragmentary fractures across the classification groups (A3 + C2 + C3), the OR of sustaining a multifragmentary fracture did not significantly differ according to BMD status (osteoporosis gave an OR of 1.4 (95% CI 0.6–3.7), and osteopenia OR 1.0 (95% CI 0.4 to 2.6)). Low energy trauma mechanism decreases the odds of comminuted fractures compared to the other AO subgroups (OR for (A3 + C2 + C3) 0.3 (95% CI 0.1–0.5)).

Discussion

The odds of sustaining a distal radius fracture Type B or C compared to Type A in patients with osteoporosis did not differ from those with osteopenia or normal BMD. This indicates that the AO classification of the fracture cannot be used to decide which patients should be referred to DXA scan and considered for secondary fracture prevention. One may argue that the AO-classification system is not able to capture all the facets of a fracture, as many factors concern the mechanical complexity and etiology of a fracture (e.g. the position and angle of the extremity and the body at the time of the fall, body composition and weight, balance, rotational forces, and the surroundings). A more detailed discussion of the classification system is beyond the scope of the current study, which aims to investigate the association between osteoporosis and the severity of distal radius fractures using established radiographic methods.

Our results are in line with previous rapports. A study including 137 patients with low-energy distal radius fractures found an inverse correlation between BMD of the hip measured 3 months after the fracture and likelihood of early instability, late carpal malalignment and malunion [10]. However, no correlation between BMD and the AO subtypes was found. The same study found that BMD in patients with type C fractures was higher than in patients with type A fractures, which is in agreement with our results. This is also supported by a study of 208 patients with distal radius fracture, where no correlation between the AO-classification and BMD of the hips and spine was found [11]. The authors suggested that a

Table 1 Characteristics of patients with distal radius fractures according to type of fracture (Müller AO classification system)

	Fracture type				
	All	AO type A	AO type B	AO type C	AO type B + C
Total n	289	92	34	158	192
Age, mean (range)	63 (40–92)	62 (42–88)	62 (42–80)	64 (40–92)	64 (40–92)
Female sex, n (%)	231 (80)	78 (85)	21 (61)	128 (81)	149 (78)
Osteoporosis[a], n (%)	130 (45)	43 (47)	10 (29)	76 (48)	86 (45)
Osteopenia[b], n (%)	95 (33)	31 (34)	13 (38)	47 (30)	60 (32)
BMI, mean (SD)	26 (5)	26 (4)	28 (5)	26 (5)	26 (5)
Overweight, n (%)	95 (33)	27 (29)	12 (35)	55 (35)	67 (35)
Obesity, n (%)	64 (22)	21 (23)	11 (32)	28 (18)	39 (21)
Current smoking, n (%)	43 (15)	20 (22)	3 (9)	19 (12)	21 (11)
Previous smoking, n (%)	121 (42)	39 (42)	11 (32)	67 (42)	64 (41)

[a] T-score ≤ − 2.5
[b] T-score − 1.0 - -2.5
AO AO classification, *BMI* Body Mass Index (BMI categories: underweight BMI < 18.5, normal weight BMI 18.5–24.99, overweight BMI 25–29.55 and obesity BMI ≥30.0); SD: Standard deviation

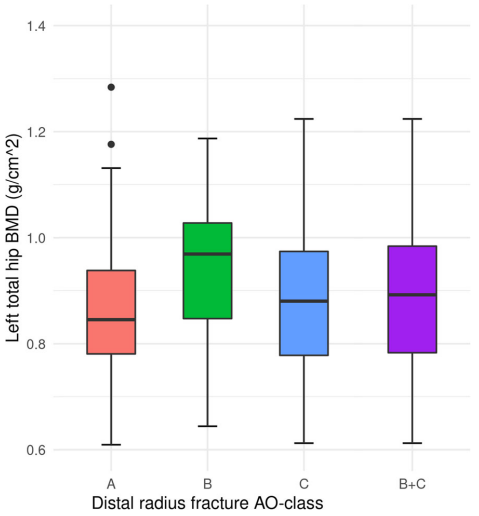

Fig. 1 Left hip total BMD measurements box plot for distal radius fracture subgroups.AO, AO classification. Centre horizontal line of the boxes represents the median. The boxes contain Q1 (25th Percentile) to Q3 (75th Percentile). IQR (Interquartile range) is the distance between Q1 and Q3. The bottom whiskers: less than Q1–1.5*IQR. The upper whiskers: greater than Q3 + 1.5*IQR. BMD measurements in 9 patients missing (left hip not measurable)

Table 2 Odds Ratios (unadjusted and adjusted) for complex (AO type B and C) vs. less complex (AO type A) distal radius fractures

	OR with 95% CI	
Exposures	**Unadjusted**	**Adjusted**
BMI	1.0 (0.8–1.3)	1.0 (0.7–1.3)
Current smoking[a]	0.4 (0.2–0.9)	0.4 (0.2–0.8)
Previous smoking[a]	0.8 (0.4–1.3)	0.7 (0.4–1.3)
Osteoporosis[b] T-score ≤ −2.5	0.8 (0.4–1.5)	1.1 (0.5–2.3)
Osteopenia[c] T-score – 1.0 - -2.5	0.8 (0.4–1.6)	1.0 (0.5–2.1)
Age > 65 years[d]	1.4 (0.9–2.4)	1.6 (0.9–2.7)
Male sex[e]	1.7 (0.9–3.5)	1.5 (0.7–3.1)
Low energy trauma[f]	0.5 (0.3–0.8)	0.4 (0.2–0.8)

OR Odds ratio, *CI* Confidence interval, *BMI* Body mass index
Relevant risk factors adjusted for were: age, sex, BMI, smoking, bone mineral density and low energy trauma
[a]Reference category was the non-smoking group. When analyzing current smoking, the group of previous smoking is removed, and vice versa
[b]Reference category was no osteoporosis (osteopenia and normal bone mineral density)
[c]Reference category was normal bone mineral density (T-score ≥ – 1.0)
[d]Reference category was age < 65
[e]Reference category was female sex
fReference category was no low energy trauma

possible explanation for this might be that DXA measures thickness of cortical bone, which is thicker in the metaphyseal area than in the epiphyseal area. A more severe osteoporotic fracture would therefore be a metaphysal fracture instead of an intra-articular fracture. Dhainaut et al. [12] assessed cortical hand BMD by digital X-ray radiogrammetry in 110 female patients with fragility fracture at the distal radius, and concluded with no correlation between neither BMD of the hip or spine nor the digital X-ray radiogrammetry and the AO fracture type. The only significant risk of intra-articular distal radius fracture compared to less complex fractures in that study was ever having used glucocorticoids, supporting the hypothesis that the severity is more associated with other factors comprising bone quality than BMD.

Severity of a distal radius fracture is a clinical assessment. The AO classification does not take into consideration instability, malunion, decreased radial length or the degree of dorsal angulation. It is clinically not clear if a complete articular fracture without displacement (C1) is more harmful to the patient than an extra-articular fracture with metaphyseal comminution (A3). Clayton et al. [10] define the most serious distal radius fracture types as A3, C2 and C3. Subanalysis of our data did not support that osteoporosis leads to a higher proportion of these fractures compared to other subtypes. We found a significantly lower OR for low energy trauma among those with type B or C fracture compared to type A. This illustrates that factors influencing fracture severity may be complex.

Strengths and limitations

Our study was not primarily designed to investigate the association between osteoporosis and radiological severity of distal radius fractures. The study was therefore underpowered to conclude on some aspects, as there are many subtypes of fractures and accordingly few fractures in some of the groups. We did, however, have a large number of patients compared to previous studies, and we included both women and men. The radiographic interpretations were done by an experienced radiologist, and the AO classification has earlier been shown to have good intra-observer reliability when restricted to the three main AO-types [17]. To our knowledge no studies have shown an association between the AO-classification, fracture severity and clinical outcome. Accordingly, based on our results the clinical severity of the fractures could not be assessed, only the radiographic complexity. A strength of this study was the availability of supplementary CT scans in 68% of the distal radius fractures. The use of CT scans may explain that there

were more AO type C fractures in our study, compared to other studies reporting more type A fractures.

Conclusions

In this study, severity of distal radius fractures according to the AO-classification of distal radius fractures was not associated with osteoporosis when adjusted for age, sex, and BMI. AO-classification of distal radius fractures cannot be used to identify which patients should be evaluated and treated for osteoporosis.

Abbreviations

BMD: Bone mineral density; DXA: Dual-energy x-ray absorptiometry; BMI: Body mass index; AO: Müller AO classification system; MOF: Major osteoporotic fracture

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Authors' contributions

Conception and design: AMH and PM. Collection and assembly of data: AMH and PM. Analysis: PM. Interpretation of the data: AMH, PM, JEG, RMN, EA. AL and GST. Drafting of the manuscript: AMH. Critical revision and final approval of the article: all authors.

Authors' information

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Availability of data and materials

Due to regulations from the Norwegian Data Inspectorate and according to Norwegian personal protection laws publication of the complete dataset is not legal or appropriate. If authors/researchers wish to have access to the dataset, this can still be achieved through direct contact with us.

Ethics approval and consent to participate

All participants signed a written informed consent form, and the study protocol was approved by the Regional Committee for Medical and Health Research Ethics (REC West).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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