Trabecular bone score and vertebral fracture assessment in patients with fragility fractures

Dissertation for the degree of Philosophiae Doctor

Tove Tveitan Borgen

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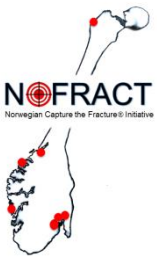

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Abbreviations

AOD	Anti-osteoporosis drugs
BMD	Bone mineral density
BMI	Body mass index
BTM	Bone turnover markers
CI	Confidence interval
CT	Computed tomography
DXA	Dual energy x-ray absorptiometry
FLS	Fracture Liaison Service
FRAX	Fracture risk assessment tool
HRT	Hormone replacement therapy
IOF	International Osteoporosis Foundation
ISCD	International Society of Clinical Densitometry
MOF	Major osteoporotic fracture
NoFRACT	The Norwegian capture the fracture initiative
OR	Odds ratio
PTH	Parathyroid hormone
SD	Standard deviation
SQ	Semiquantitative deformity
TBS	Trabecular bone score
VFA	Vertebral fracture assessment
WHO	World health organization

Summary

Background

Trabecular bone score (TBS), vertebral fracture assessment (VFA) and bone mineral density (BMD) affords information of bone strength and fracture risk. Further understanding of the contribution of each of them in post-fracture risk assessment is of interest to improve identification of individuals at high risk of subsequent fractures and to set screening strategies for fracture patients. In patients with recent fragility fractures, we studied risk factors for fracture, TBS, prevalence of semiquantitatively assessed vertebral fractures (SQ1-SQ3 fractures) using VFA and assessed BMD using dual energy x-ray absorptiometry. The objectives were to explore i) the clinical characteristics, prevalence of low TBS and SQ1-SQ3 fractures in patients with fractures, ii) the differences between the sexes and between patients with and without vertebral fractures, iii) the risk factors for fractures including TBS, proportion of SQ1-SQ3 fractures and BMD in patients with different types of fragility fractures, iv) the differences between patients with central and peripheral fractures and v) the determinants of TBS and SQ1-SQ3 fractures and the interaction between these.

Methods

This cross-sectional study included a total of 839 women and men above 50 years of age who recently had sustained a fragility fracture. A total of 771 had TBS calculated, 679 had VFA performed, 804 had BMD of the total hip, femoral neck and/or spine, and 696 had responded to a questionnaire about risk factors for fracture. Paper I included all these patients. Of these, 495 women and 119 men who all had valid measurement of TBS, VFA and BMD of the femoral neck, total hip and lumbar spine were included in paper II. Paper III included 496 women who all had responded to a questionnaire about risk factors for fracture, had valid measurements of TBS and BMD of femoral neck and/or lumbar spine and 423 had VFA performed.

Results

Paper I: The mean age of the patients was 65.8 years and 80.5% were women. The prevalence of low TBS (≤ 1.23) was 34.0% and 34.8% had SQ1-SQ3 fractures. The proportion of patients with osteoporosis (BMD T-score ≤ -2.5) at the femoral neck was 13.8% and the skeletal site with lowest BMD T-score 27.4%. Women exhibited lower mean TBS and lower BMD at all sites than men. Patients with SQ1-SQ3 fractures were older, had lower TBS and lower BMD at all sites than those without SQ1-SQ3 fractures (all $p < 0.05$).

Paper II: Patients with centrally sited fractures exhibited lower mean TBS and a higher proportion of both SQ1-SQ3 fractures, SQ2-SQ3 fractures and SQ3 fractures and lower BMD of the femoral neck, total hip and lumbar spine than patients with peripherally sited fractures (all $p < 0.05$).

Paper III: Higher age, a history of parental hip fracture and daily alcohol intake were associated with lower TBS. Higher BMD of the femoral neck and lumbar spine were associated with higher TBS. Age and prior fragility fractures were positively associated with SQ1-SQ3 fractures, while lumbar spine BMD was negatively associated with SQ1-SQ3 fractures. No association between TBS and SQ1-SQ3 fractures was found.

Conclusions

More than half of the patients with fragility fractures had SQ1-SQ3 fractures, low TBS or both. Patients with central fragility fractures exhibited lower TBS, a higher prevalence of SQ1-SQ3 fractures and lower femoral neck BMD than patients with peripheral fractures. This suggests that patients with central fragility fractures have a higher risk of subsequent fractures and should get the highest priority in secondary fracture prevention. No association between TBS and SQ1-SQ3 fractures was found; hence they may act as independent risk factors, justifying the use of both in post-fracture risk assessment.

Sammendrag

Bakgrunn

Trabekulær ben skår (TBS), vertebral fraktur bedømmelse (VFA) og benmineraltetthet (BMD) gir informasjon om skjelettstyrke og bruddrisiko. Dypere forståelse av hvilket bidrag hver av disse gir til risikovurdering etter lavenergibrudd er av interesse for å bedre kunne identifisere individer med høy risiko for nye brudd og for å legge strategier for screening av bruddpasienter. Vi studerte risikofaktorer for brudd, TBS, prevalens av semikvantitativt angitte ryggbrudd (SQ1-SQ3 brudd) ved VFA og BMD målt med røntgenbasert absorpsjonsmetri hos pasienter som nylig var blitt behandlet for lavenergibrudd. Hensikten var å kartlegge i) kliniske karakteristika, prevalens av lav TBS og SQ1-SQ3 ryggbrudd hos pasienter med lavenergibrudd, ii) forskjeller mellom kjønn og mellom pasienter med og uten ryggbrudd, iii) risikofaktorer for benbrudd inkludert TBS, SQ1-SQ3 brudd og BMD hos pasienter med ulike typer lavenergibrudd, iv) forskjeller mellom pasienter med sentrale og perifere brudd samt v) determinanter for TBS og SQ1-SQ3 brudd og interaksjonen mellom disse.

Metoder

Denne tverrsnittstudien inkluderte 839 kvinner og menn i alderen 50 år eller eldre, som nylig var blitt behandlet for lavenergibrudd. Tilsammen 771 hadde beregnet TBS, 679 hadde tatt sidebilde av ryggsøylen for VFA, 804 hadde målt BMD av lårhals, total hofte og/eller rygg, og 696 hadde besvart spørreskjema om risikofaktorer for benbrudd. Artikkel I omhandlet alle disse pasientene. Av disse inkluderte vi 495 kvinner og 119 menn som alle hadde valid måling av TBS, VFA, og BMD av lårhals, total hofte og lumbalcolumna i artikkel II. Artikkel III inkluderte 496 kvinner som alle hadde besvart spørreskjema vedrørende risikofaktorer for brudd, som hadde fått beregnet TBS, målt BMD av lårhals og/eller lumbalcolumna og 423 kvinner som hadde utført VFA.

Resultater

Artikkel I: Pasientenes gjennomsnittsalder var 65,8 år og 80,5% var kvinner. Prevalens av lav TBS (≤ 1,23) var 34,0% og 34,8% hadde SQ1-SQ3 brudd. Andelen pasienter med osteoporose (BMD T-skår ≤ -2,5) var 13,8% i lårhals og 27,4% i måleområdet med lavest BMD T-skår. Kvinner hadde lavere gjennomsnittsverdi for TBS og lavere BMD på alle måleområder enn menn. Pasienter med SQ1-SQ3 brudd var eldre, hadde lavere TBS og lavere BMD på alle måleområder og enn pasienter uten SQ1-SQ3 brudd (alle $p < 0,05$).

Artikkel II: Pasienter med sentralt lokaliserte benbrudd med hadde lavere gjennomsnitts TBS og høyere andel pasienter med SQ1-SQ3 brudd, SQ2-SQ3 brudd og SQ3 brudd, samt lavere BMD målt både i lårhals, total hofte og i lumbalcolumna enn pasienter med perifert lokaliserte benbrudd (alle $p < 0,05$).

Artikkel III: Høyere alder, historie med foreldre med hoftebrudd og daglig alkoholinntak var assosiert med lavere TBS. Høyere BMD i lårhals og lumbalcolumna var assosiert med høyere TBS. Alder og tidligere lavenergibrudd var positivt assosiert med SQ1-SQ3 brudd, mens BMD i lumbalcolumna var negativt assosiert med SQ1-SQ3 brudd. Det ble ikke funnet noen assosiasjon mellom TBS og SQ1-SQ3 brudd.

Konklusjoner

Mer enn halvparten av pasientene med lavenergibrudd hadde SQ1-SQ3 brudd, lav TBS eller begge deler. Pasienter med sentralt lokaliserte brudd hadde lavere TBS, høyere prevalens av SQ1-SQ3 brudd og lavere BMD i lårhals enn pasienter med perifert lokaliserte brudd. Dette kan bety at pasienter med sentrale brudd har høyere risiko for nye brudd og derfor bør prioriteres først i sekundærforebygging av brudd. Det ble ikke funnet noen assosiasjon mellom TBS og SQ1-SQ3 brudd, hvilket kan tolkes som at de fungerer som uavhengige risikofaktorer og derfor har begge en plass i bruddrisikovurdering hos pasienter etter lavenergibrudd.

List of publications

Paper I

Borgen TT, Bjørnerem Å, Solberg LB, Andreasen C, Brunborg C, Stenbro M-B, Hübschle LM, Froholdt A, Figved W, Apalset EM, Gjertsen J-E, Basso T, Lund I, Hansen AK, Stutzer J-M, Dahl C, Omsland TK, Nordsletten L, Frihagen F and Eriksen EF.

"High prevalence of vertebral fractures and low trabecular bone score in patients with fragility fractures: A cross-sectional sub-study of NoFRACT"

Bone 122 (2019)14-21.

Paper II

Borgen TT, Bjørnerem Å, Solberg LB, Andreasen C, Brunborg C, Stenbro M-B, Hübschle LM, Froholdt A, Figved W, Apalset EM, Gjertsen J-E, Basso T, Lund I, Hansen AK, Stutzer J-M, Omsland TK, Nordsletten L, Frihagen F and Eriksen EF.

"Post-Fracture Risk Assessment: Target Centrally Sited Fractures First! A Sub-Study of NoFRACT"

J Bone Miner Res (2019) 34(11):2036-44.

Paper III

Borgen TT, Bjørnerem Å, Solberg LB, Andreasen C, Brunborg C, Stenbro M-B, Hübschle LM, Figved W, Apalset EM, Gjertsen J-E, Basso T, Lund I, Hansen AK, Stutzer J-M, Dahl C, Nordsletten L, Frihagen F and Eriksen EF.

"Determinants of trabecular bone score and vertebral fractures in women with fragility fractures. A sub-study of NoFRACT"

Osteoporos Int (2019) Nov 21 [Epub ahead of print]

1 Introduction

1.1 Osteoporosis and bone fragility

Osteoporosis is the medical term of bone fragility. The word “osteoporosis” consists of the two Greek words “ostó” (οστό) which means bone and “poródis” (πορώδης) which means porous. The current definition of osteoporosis was established at the National Health Institute Consensus Conference in 2001 (1):

> “Osteoporosis is a skeletal disorder characterized by
> compromised bone strength predisposing to an increased risk of fracture.
> Bone strength reflects the integration of two main features:
> Bone density and bone quality”.

This definition includes all skeletal factors that underlie compromised bone strength. Bone mineral density (BMD), which is a quantification of the amount of mineral in bone, explains about 60-70% of bone strength (2). The bone properties contributing to bone strength which BMD reflects is: geometry (the size of the bone that is scanned), cortical and trabecular architecture (reflected by amount of mineralized bone) and mineralization of bone matrix. Bone quality is another aspect of bone strength defined by: bone material properties (i.e. collagen and osteocyte density) and bone structural properties (microarchitecture in cortical and trabecular bone beyond mineralization, and accumulation of micro cracks)(3). Additionally, bone strength is also influenced by bone turnover.

The diagnostic criterion of osteoporosis adopted by the World Health Organization (WHO) in postmenopausal women from 1994 are based solely on the measurement of BMD (4). BMD T-score describes how many standard deviations (SD) the BMD value departs from the mean of the young adult reference range. Osteoporosis is defined as BMD T-score of -2.5 SD or less. BMD T-score ranging between -1.0 and -2.5 is defined as osteopenia and normal BMD as BMD T-score equal to and above -1.0.

"Osteoporosis is defined by the presence of a bone mineral density 2.5 standard deviations or less
below the mean bone density of young, white adult women".

The WHO criterion was primarily intended for descriptive epidemiology of prevalence of osteoporosis in different sexes, countries and races. For this purpose, standardization of measurement site and reference population was important. BMD of the femoral neck was chosen as the standard site for measuring BMD, since BMD at this site differed least between the dual x-ray absorptiometry (DXA) equipment used (5). The recommended reference population was the Third National Health and Nutrition Examination Survey (NHANES III) population of young adult women, to be used for both women and men (5). The strength of this diagnostic criterion is the high specificity, as low BMD is one of the strongest predictors for fracture (6, 7). However, the sensitivity is low, since most of the fragility fractures occur in patients with osteopenia, not in those with osteoporosis (8, 9). Despite this, osteoporosis defined as BMD T-score of -2.5 or below is used worldwide as intervention threshold for treatment and reimbursement criterion for treatment, whereas osteopenia is not.

The prevalence of osteoporosis among Scandinavian women is high. A Norwegian study from 2012 showed that 24% of women between 60 and 70 years and 37% of women between 70 and 80 years had osteoporosis (10). Data from the Tromsø Study showed lower prevalence of osteoporosis in men than in women (11). This was also shown in Swedish data, with an increasing prevalence with age for both sexes (Fig. 1)(12).

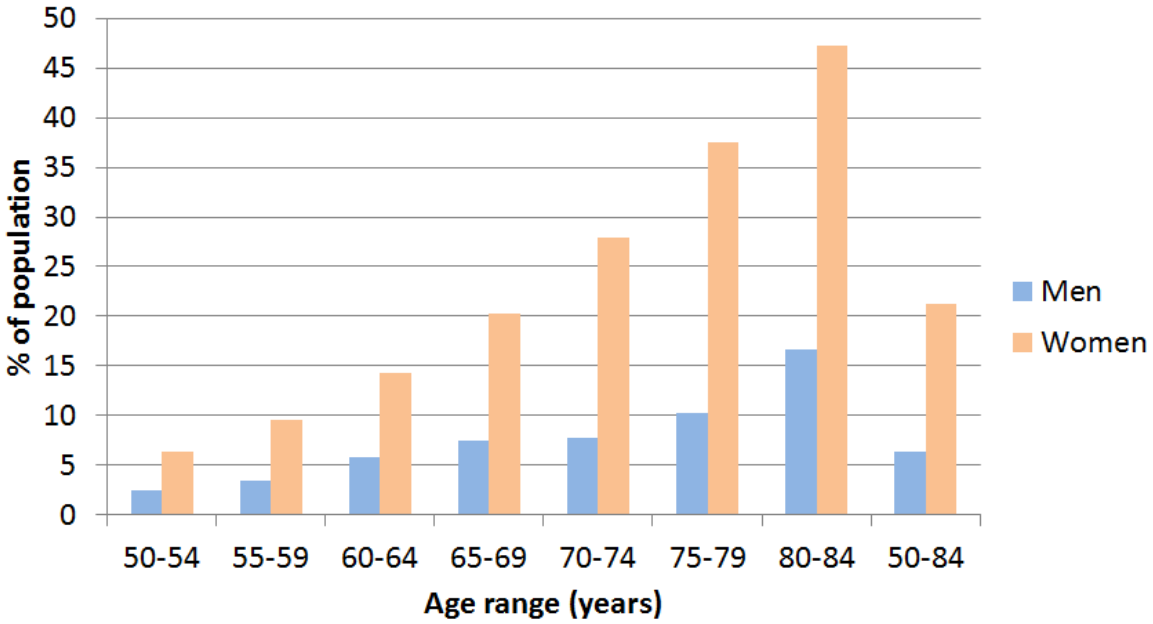


Fig. 1. Prevalence of osteoporosis at the femoral neck in Sweden in different age groups. Reproduced from Kanis et al. 2000 with permission.

1.2 Fragility fractures and osteoporotic fractures

Osteoporosis is a silent disease presenting no symptoms before a fracture occurs. There are two approaches to describe fractures that are associated with osteoporosis. One approach is to describe all fragility fractures as osteoporotic. A fragility fracture is defined as a fracture that arises spontaneously or after a minimal trauma that normally would not have caused fracture, for instance after a fall from standing height (13). Fragility fractures are also called "low-energy fractures", describing that the traumas causing these fractures involve little or no energy as opposed to high-energy traumas such as a car accident or fall from a height.

The other approach is to define osteoporotic fractures as fractures strongly associated with low BMD and with increasing incidence after the age of 50 years. Vertebral fractures, fractures of the forearm, hip and proximal humerus are associated with low BMD, and they are termed "major osteoporotic fractures (MOF)" (14).

A fragility fracture is a symptom of underlying impaired bone strength. It can be challenging to determine in each case whether the fracture is caused by a low-energy trauma or not, since the mechanism of injury varies. Complementary information about the trauma is often lacking. Therefore, MOF are more often used as variable in osteoporosis research.

1.3 Epidemiology and the burden of fragility fractures in Norway

Bone fragility is a global health problem with more than nine million fractures annually (15). For largely unknown reasons, Norway has among the highest rate of hip and forearm fractures in the world (16, 17). Every year, about 10 000 women and men above 50 years of age suffer a hip fracture (18, 19) and 15 000 a forearm fracture (17). Hip fractures are estimated to constitute about 20% of all osteoporotic fractures in Europe (15), hence the annual number of osteoporotic fractures in Norway is probably around 50 000. The exact number is lacking. The remaining lifetime risk of osteoporotic fractures in women and men above 50 years of age is 46% and 22%, respectively (20).

Due to increasing life time expectancy in the population, the number of elderly is increasing (21). The annual number of fractures and associated costs are expected to increase by 50% between 2005 and 2050 (22, 23). Even if hip fracture rates in Norway remain constant, the annual number of hip fractures is expected to double towards 2040 (24). This represents substantial health and socioeconomic challenges. Fragility fractures, especially hip and vertebral fractures, are associated with a considerable burden of morbidity such as pain, loss of function, disability, hospitalization, and long-term nursing care (25, 26). Mortality is also increased after certain fragility fractures. Data from the population-based Tromsø Study showed a two-fold increase in mortality after hip fractures and 49% and 81% increased mortality rate in women and men, respectively following a proximal non-hip non-vertebral fracture (27). The estimated costs of the annual 2.7 million fragility fractures in Europe is 36 billion Euro (26). In Sweden, the direct annual costs related to fractures has been estimated to 5.6 billion SEK (28). Including public services as nursing homes and quality-adjusted life-years (QALYs) lost, the annual societal burden of fragility fractures in Sweden was 15.2 billion SEK in 2005 and is expected to increase to 26.3 billion in 2050 (28). There are no good estimates of the total costs of osteoporotic fractures in Norway, but probably the amount is the half of that of the Swedish expenses,

since the Norwegian population is half the size with similar fracture rate as the Swedish. Folkehelsemeldingen 2012/2013 refers to hip fractures as one of the most expensive diagnoses for the Norwegian health system, and the total costs during the first year after a hip fracture is estimated to 500.000 NOK (29).

Vertebral fractures are the hallmark of osteoporosis and one of the most common osteoporotic fractures. The incidence and prevalence increase with age and is higher in the Scandinavian population compared to the other European countries (27). Prevalent vertebral fractures are the fractures found by radiological imaging of the spine. Once a vertebral fracture has occurred, it is irreversibly deformed; hence, the prevalent vertebral fractures found can be of any age. The prevalence of vertebral fractures in population-based studies in women and men above 70 years in Norway has been estimated to 19-20% using vertebral fracture assessment (VFA) of lateral DXA scans (30). Using the Eastell method and McCloskey method to identify vertebral fractures on x-rays of thoracolumbar spine, the prevalence of vertebral fractures was found to be 22% and 16% in men and 24% and 19% in women, respectively (31). Vertebral fractures are associated with considerable impact on quality of life, disability, morbidity, mortality and socioeconomic costs (23, 32).

1.4 The care gap

Despite the high economic cost to society and personal cost to affected individuals, osteoporosis prevention has been suboptimal in Norway as in the rest of the world. The prevalence of osteoporosis among Norwegian women is high. One in four women between 60 and 70 years has osteoporosis and more than one in three women between 70 and 80 years (10). In these age groups, only 4% and 10% are treated with anti-osteoporosis drugs (AOD), respectively. Among Norwegian women aged 50 years and above with distal forearm fracture, 31% meet the diagnostic WHO criteria of BMD T-score ≤ -2.5 (33). In a

study of Norwegian patients with hip fractures from 2012, only 15% of women and 4% of men received AOD after the fracture (34). Many patients with a high risk of fractures do not receive available and efficient therapy (22) although AOD are readily available and may reduce the risk for future fracture by 30-50% (35, 36).

To reduce this treatment gap, the International Osteoporosis Foundation's (IOF) has promoted the campaign "Capture the Fracture" (37) to encourage secondary fracture prevention. The fracture liaison service (FLS) model of care is central in this intervention. Dedicated FLS nurses perform a systematic approach to secondary fracture prevention, by identifying, assessing and recommending treatment to patients with fragility fracture who are at high risk of subsequent fractures (38). Additional life style advice should be given if needed concerning physical activity, healthy diet, moderation of alcohol intake and smoking cessation. The FLS model of care is widely recommended, but large data on its effectiveness regarding reduced re-fracture risk and fractures related mortality are scarce. There are promising studies, like the Glasgow study, which showed a reduction of hip fracture rate by 7% after introducing FLS, while the rate increased by 17% in the rest of England (39). A study of the effect of introducing a Minimal Trauma Fracture Liaison Service in Sydney in 2005, showed 80% lower incidence of new fractures in the patients enrolled in the program compared to controls (40). At Skåne Universitetssjukhus, Lund, the re-fracture rate was reduced by 42% after introduction of osteoporosis assessment of patients with fragility fractures (wrist, shoulder, vertebral, or hip fracture), and mortality after fractures was slightly reduced (41, 42).

1.5 Risk factors for fractures

Osteoporosis is a multifactorial disease with a complex etiology of interactions between genetic, environmental and metabolic factors. Fracture risk is also multifactorial, and a broad approach is therefore necessary in fracture risk assessment. Information about as many risk factors as possible is of interest, and the most important are age, sex, BMD and a history of prior fractures.

1.5.1 Age and sex

Age is a major risk factor for fractures. Age-related bone loss is a result of unbalanced remodelling of bone in the bone modelling units at the surface in both trabecular and the cortical bone (43). In trabecular bone, the plate like trabeculae become first rod like, and with increasing bone loss they disrupt and are irreversibly lost (43). Therefore, this bone loss is after some time self-limiting (44). In cortical bone, the net resorption occurs at the intracortical surface of the Haversian channels, which increase in width, resulting in increased cortical porosity (45). In addition, there is a net resorption at the endosteal bone surface resulting in thinning of the cortex from inside and a wider marrow cavity, and with corresponding periosteal bone formation, resulting in increased diameter of long bones (43). Since the surfaces of the cortical bone increases with increasing bone loss, this bone loss is self-perpetuating with age (44). In other words; *volume* bone loss is mainly trabecular in early osteoporosis and becomes primarily endo- and intracortical with increasing age (46). The annual loss of bone mass is largest in women during and after menopause. About 80% of the bone *mass* which is lost in women transitioning from pre to postmenopausal stage is cortical (47). This may explain why 80% of the fractures are appendicular. With increasing age, additional risk factors for fracture also protrude, such as further decrease in BMD, impaired quality of bone, increased tendency to fall, more previous

fractures, less physical activity and more comorbidity. The risk of hip fractures increase about 40-fold from 50 to 80 years, compared to a 4-fold increased gradient of risk estimated by BMD (48).

Female sex is also a major risk factor for fractures, with menopause as the single most important risk factor. Women have a smaller skeleton than men with lower BMD and smaller cross-sectional area of the knuckles, resulting in a higher fracture risk (49). The difference in BMD between the sexes increases due to decreasing estradiol in women at menopause, leading to an annually net bone loss of 1-3% during the first 10 years after menopause. It is estimated that 22 million women and 5.5 million men have osteoporosis in Europe based on BMD of the femoral neck (23). In other words, osteoporosis is 4 times more common in women than in men. A 50-year old women has a 44% lifetime risk of a fracture, while a man at the same age has a risk of 25% (50).

1.5.2 Bone Mineral Density

Measurement of BMD by DXA is the most common approach used to assess fracture risk and is considered the gold standard as a surrogate for bone strength (51, 52). X-rays of two different intensities are emitted through the patient; the density of the soft tissue is subtracted, making it possible to estimate the calcium content of the bone tissue, i.e. BMD per unit area (areal density, g/cm^2). This two-dimensional imaging of a three-dimensional knuckle is therefore influenced by the geometry and bone size as well. The volumetric bone density in a small and a large knuckle might be the same, but the two-dimensional BMD is higher in the large knuckle due to the larger size (53).

The incidence of almost all types of fractures increases with decreasing BMD (54) and BMD turns out to be an equally important risk factor in both sexes. Women and men fracture at the same absolute BMD (9). Low BMD predicts best the fractures at the site that is measured (6, 55). For instance, low femoral neck

BMD predicts better hip fractures; low lumbar spine BMD predicts better vertebral fractures (56) and low BMD of ultra-distal radius predicts distal forearm fractures (57). Several population-based studies have demonstrated that for each SD decrease in BMD below the normal mean BMD, there is roughly a two fold increase in risk of a subsequent hip fracture (58).

In the prospective Study of Osteoporotic Fractures, 9704 patients with BMD measured at both central and peripheral sites were followed for ten years (54). A decrease in lumbar spine BMD was primarily associated with increased risk of upper central fractures (spine, humerus and clavicle), whereas a decrease in hip BMD showed a stronger association with central fractures (hip, spine, humerus, pelvis, femur). A decrease in peripheral BMD was associated with increased risk of peripheral fractures (BMD of distal radius was associated with increased risk of fractures of wrist, humerus, hand and lower leg, whereas BMD of calcaneus was associated with fractures of humerus, lower leg, patella, heel, femur, and hand)(54).

International Society of Clinical Densitometry (ISCD) recommends central DXA of femoral neck, total hip or lumbar spine for assessment of BMD, and osteoporosis is diagnosed if the BMD T-score is of -2.5 or less at one of these sites (59). However, bone fragility can be present at a higher level of BMD T-score than -2.5, confirmed by the fact that most patients with fragility fractures exhibit BMD in the non-osteoporotic range (8, 9, 60-62).

1.5.3 History of prior fractures

A history of a prior fragility fracture doubles the risk of a new fracture. A hip fracture increases the risk of a new hip fracture three times (25, 26) and a vertebral fracture increase the risk for a new vertebral fracture up to seven times (26). Vertebral fractures are strong predictors of new vertebral fractures

and hip fractures (63). The fracture risk also increases by the number of prior fractures.

The fracture rate increases with age and the type of fracture also alter with age. Forearm fracture is most common fracture in the 5th and 6th decennium, whereas hip fracture is the most common fracture after the age of 75 years (64). The reasons can be different fall mechanism in younger and elderly adults (65) and differential loss of cortical and trabecular bone at different stages of aging (64).

The risk of a subsequent fracture is highest the first years after a MOF and increases with age (66, 67). After a hip fracture, about 75% of re-fractures occur within five years (68). In a study of over 350,000 American women > 65 years of age, the highest risk of subsequent fractures was found after an initial fracture at a central site such as vertebral, hip, pelvis or clavicle (69). This high risk of new fracture within the first years after a fracture is called the imminent fracture risk.

1.5.4 Heredity, anthropometry, lifestyle, comorbidity and medication

The etiology of osteoporosis is complex, consisting of inherited, environmental and metabolic factors. In recent years, osteoporosis has been considered a multifactorial, polygenic disease modified by hormonal, nutritional and environmental factors (70). Several studies have demonstrated that there are associations with genetic predisposition, race, and ethnicity and incidence of osteoporosis and fragility fractures. Caucasians have lower BMD than Africans, Hispanic and Latin-Americans (5). Heritability of BMD is estimated between 50% and 85% (71, 72). Genetics are estimated to explain about 25%, 45-54% and 48% of the variance in osteoporotic fractures, wrist and hip fractures, respectively (73). Having a first degree relative with osteoporosis or a parent with a history of hip fracture is considered a risk factor for fracture.

More than 100 different loci are identified by genome-wide association studies (GWAS) and collectively explain less than 6% of the variance in BMD (70) and 10-20% of the variance in bone phenotypes (72). Additionally, several loci associated with other features important for bone metabolism such as receptor activator of nuclear factor kappa-B (RANK) ligand, osteoprotegrin (OPG), wingless Int-1 (WNT) signaling, sclerostin, Dickkopf, estrogen receptors and vitamin D receptor, are identified. The genetics of most of the fractures seem to be mediated through genetic influence on BMD (72). Advancing technology is expected to expand the knowledge in this field in the future.

Another aspect of heritable traits is height. An association between height and increased fracture rate has been shown (74, 75). One explanation is heavier loads imposed to bone during a fall. In hip fractures, an explanation might also be a longer hip axis length and longer arm of the weight momentum. Taller individuals have longer and wider bones with a relatively thinner cortex (76, 77), which also become more porous with age (77). There are also associations between body mass index (BMI) and fracture risk, mostly acting through interaction between BMI and BMD. Low BMI is associated with increased risk of fragility fractures (75), on the other hand, obesity has been found to be associated with an increase in fractures of the ankle, crus and humerus (78).

Physical activity has a positive influence on all organs of the body, including the skeleton (79). During childhood and adolescence, physical activity is crucial to gain optimal peak bone mass. In adults and the elderly, physical activity can prevent or reduce bone loss, especially postmenopausal bone loss in women. The skeleton adapts physiologically to the external forces it is exposed to. In general, exercise has a small, but possibly important effect on BMD in postmenopausal women (80). Progressive resistance training of the lower limbs has a positive effect mainly on femoral neck BMD, whereas multi component exercise programs mainly has a positive effect on lumbar spine BMD (81). An improvement in BMD has also been shown after exercise with vibrating

platforms and weight-bearing aerobic training (81). Moreover, physical activity, with improvement of muscle strength and balance, will also have a positive effect on preventing falls.

Healthy nutrition is essential for both modelling and remodelling of bone. Basically, the skeleton is constantly in need for the components of which the bone is built of: Proteins and minerals (the most abundant are calcium, magnesium and phosphate). Vitamin D is important for intestinal absorption and renal reabsorption of calcium, in addition to mineralization of bone. In bone, vitamin K is a cofactor for osteocalcin and matrix Gla protein which is involved in mineralization of bone (82) and vitamin C is important in synthesis of protein. A one-sided diet, with insufficient energy, proteins, minerals and vitamins is considered a risk factor for fracture.

Current smoking increases the risk of osteoporotic fractures, and former smoking increases the risk of humerus fractures (83) without significantly alterations in BMD. Alcohol has direct toxic effect on bone cells. Alcohol intake of three or more units per day is associated with increased risk of fractures (84).

A number of diseases are associated with low BMD and increased fracture risk. The mechanisms of bone involvement can be due to inflammation (i.e. rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondyloarthritis, inflammatory bowel diseases and inflammatory lung diseases), malabsorption (i.e. celiac disease, post-bariatric surgery and inflammatory bowel diseases), hormonal disturbances (i.e. hypogonadism, hyperparathyroidism, hyperthyreosis and diabetes mellitus), renal diseases and vitamin D deficiency. Some medications are associated with low BMD or increased risk of fracture; the most well-known are corticosteroids, aromatase inhibitors, androgen deprivation agents and some anticonvulsants (especially enzyme-inducing agents).

1.5.5 Falls

Bone fragility is the major underlying cause of fragility fractures; however increased risk of falls enhances this risk of fracture (84). One in three persons above 65 years of age falls one or more times per year (85), and women fall more often than men. However, only about 5% of the falls lead to fractures.

Increased tendency to fall

Patient related factors:
Impaired balance
Slower reflexes
Muscle weakness
Impaired vision
Low blood pressure
Multi pharmacy
Psycho pharmacy
Seizures
Arrhythmias
Dementia

Environmental factors:
Icy or slippery underlay
Not proper shoes/soles
Stumble traps
Poor lightning
Sudden unexpected events

1.5.6 Fracture risk assessment tools

As fracture risk is highly multifactorial, risk assessment tools have been developed to calculate 10-year fracture risk by including a various number of risk factors, with and without including BMD. The best known tools are Fracture Risk Assessment Tool (FRAX) (84) and Garvan nomogram (86).

FRAX calculates the 10-year probability of a major osteoporotic fracture or hip fracture based on clinical risk factors as sex, age, height, weight, previous fracture, parental history of hip fracture, smoking, excessive alcohol intake, glucocorticoid therapy, rheumatoid arthritis and other causes of secondary osteoporosis, with and without including femoral neck BMD (84, 87). Additionally, FRAX takes into account the competing risk of death so the probability of fracture will decrease when approaching the age of life expectancy. The FRAX model is built on Poisson regression models, which allow the interaction between clinical risk factors for fracture, death and age. For instance, BMI or smoking influences not only the fracture risk but also the risk of death. This is not taken into account in other fracture prediction tools.

Garvan nomograms is based on fewer risk factors and includes sex, age, number of prior fractures, number of falls the last year and can be used with or without femoral neck BMD (86). Both FRAX and Garvan nomograms are easy available online. While FRAX yields probability of fracture, Garvan estimates the absolute fracture risk. Thus the ability of these algorithms to predict fractures cannot be compared directly because of these differences (88). However, it seems that both FRAX and Garvan underestimated the observed fracture risk (low sensitivity), but Garvan has shown a higher specificity of identifying the individuals who fracture (89).

1.5.7 Trabecular bone score

Trabecular bone score (TBS) is a measure of a bone structure textural index that is obtained from the lumbar spine (L1-L4) DXA scans (90). TBS can be calculated using the iNsight software immediately after the DXA scan or retrospectively in previously obtained images. The variation in grey-level tone between the pixels in the scan is analyzed and a unit-less TBS value is calculated. A scan of a normal vertebra gives an image with a variation of pixels in the lighter zone of the grey scale, which results in a high TBS. A vertebra with deteriorated microarchitecture has a pixel variation of darker zones with little mineralization and zones with more mineralization, which gives a lower TBS. TBS has been shown to be associated with trabecular thinning, trabecular number and distance between the trabeculae in cadaver bone (91). TBS also have the ability to differ between two DXA scans with the same BMD but with different microarchitecture (92, 93). In the official positions of ISCD from 2019 it is stated that "TBS provides an indirect assessment of trabecular microarchitecture" and that "BMD measures bone quantity and TBS measures bone quality" (94). However which bone properties TBS actually reflects, is still subject to discussion (95).

Like BMD, TBS is an age-depended variable and decreases after the age of 45 years, and more marked in women than men. TBS is lower in women, in individuals with femoral neck osteoporosis, chronic obstructive pulmonary diseases, diabetes, alcohol abuse, prior fractures, glucocorticoid use and rheumatoid arthritis and higher in individuals who have been treated with AOD (96). TBS is less influenced by spondylosis of L1-L4 than BMD (97).

TBS predicts fragility fractures in both women and men independently of BMD (98-101). In the Manitoba study, which is the largest ongoing population study on TBS, 33 341 women with mean age of 63 were followed for 4.7 years. An 18% increase in MOF and 20% increased risk of death was observed for each SD decrease in TBS after adjustment for clinical risk factors and total hip BMD. The

risk of MOF in patients with TBS in the 10th percentile was 1.5-1.6 higher than for patients with TBS in the 90th percentile. Further, in this study TBS was negatively associated with prior MOF, glucocorticoid use, rheumatoid arthritis, high alcohol intake, chronic obstructive pulmonary disease and BMI and positively associated with lumbar spine and femoral neck BMD (102). The Manitoba study is important, since it is the largest cohort studied with TBS. Together with 13 other prospective population-based cohorts; this is the basis for the reference values of TBS (103).

TBS has also been shown to predict MOF independently of FRAX (103), and is therefore included in the FRAX score calculator. It is now possible to obtain FRAX score adjusted with TBS (99). TBS and lumbar spine BMD has also been shown to predict fractures equally well, and the combination of these are shown to perform better than each factor alone (98, 104, 105).

TBS is valuable for predicting fractures in conditions of secondary osteoporosis such as glucocorticoid induced osteoporosis (106), rheumatoid arthritis (107), diabetes mellitus (108), hyperparathyroidism (93) and kidney disease (109). In fact, TBS predicts fractures better than BMD in some conditions of secondary osteoporosis, such as rheumatoid arthritis, primary hyperparathyroidism, chronic kidney disease androgen-deficiency, in hormone-receptor positive breast cancer treatment and hemochromatosis (110).

Still TBS has a limited value in monitoring treatment efficacy compared to BMD, since the magnitude of change in TBS is smaller, especially when assessing effects of anti-resorptive drugs (99). ISCD state in their position paper of 2015, that TBS should not be used alone for treatment decision, since there is no evidence supporting the TBS threshold, at which subjects benefit from treatment (100).

1.5.8 Vertebral fracture assessment

Prevalent vertebral fractures, even asymptomatic, provide important information about risk of subsequent fractures. Only 7-30% of vertebral fractures are known to the patients (111-113). Lateral imaging of the thoracolumbar spine with DXA for vertebral fracture assessment (VFA) is a quick, easily accessible and informative method of identifying prevalent vertebral fractures (114). It has a specificity of 96-99% and a sensitivity of 70-84% compared to conventional x-ray in revealing subtle deformation (115). Another advantage is the lower radiation dose of 3 μSV and 9μSV in DXA Prodigy and iDXA, compared to 600μSV associated with conventional lateral X-rays of the spine (116, 117). The visual semiquantitative (SQ) method of Genant et al. is one of the most widely used techniques to diagnose vertebral fractures in radiology. This method is also recommended by ISCD for VFA of images obtained by DXA (115). Some prefer to use an algorithm-based qualitative method (ABQ) which includes an obligate central endplate affection to diagnose a vertebral deformity as fractured (118), but it is more time consuming.

VFA shows the same limitations in identifying mild compressions and assessment of vertebrae cranial to T4 as radiographs. VFA is recommended in the Capture the Fracture Best Practice Standards as a part of the assessment of patients with fragility fracture (37). Vertebral fractures predict subsequent fractures independently of BMD. Therefore, VFA should be considered in individuals with high fracture risk. ISCD recommends VFA in patients with high age (women ≥ 70 years, men ≥ 80 years), height loss (women ≥ 4cm, men ≥ 6 cm), unexplained back pain, kyphosis, and use of glucocorticoids (prior or current use) and in cases with two or more other risk factors for vertebral fracture (119).

2 Rationale and aims

More than half of the patients who have sustained a fragility fracture reveal BMD T-scores in the osteopenic range (8, 9), but they still carry a doubling in risk of subsequent fracture. Since TBS and VFA easily can provide supplemental information to BMD, we wanted to investigate which diagnostic contribution these modalities could have in a cohort of Norwegian women and men with fragility fracture.

Further, capturing all patients with fragility fractures systematically leads to a huge amount of patients with variable risk of new fractures. Prioritizing patients with the highest fracture- and mortality risk is therefore of interest. One approach could be to prioritize the patients according to fracture type. Therefore, we wanted to investigate if BMD, TBS and VFA could identify patients with types or groups of fractures, with a higher risk of subsequent fracture.

Identification of determinants of TBS and vertebral fractures is important to understand the pathophysiology and to identify modifiable risk factors for fracture. To our knowledge, this has not been studied in patients with fragility fractures before, and therefore we wanted to explore this further in the women in our cohort. As we in paper I also found that many patients had low TBS, without simultaneously vertebral fractures, we wanted to explore the association between TBS and prevalent vertebral fractures further.

The aims we sought to explore were:

Paper I:

i) To examine the clinical characteristics of a cohort of Norwegian women and men with fragility fractures, along with their prevalence of low TBS and prevalence of vertebral fractures using VFA.

ii) To explore the differences in TBS and BMD T-score between sexes and between patients with and without prevalent vertebral fractures.

Paper II:

i) To investigate the risk factors for fractures including TBS, proportion of vertebral fracture using VFA and BMD in patients with different types of fragility fractures.

ii) To explore the differences between central and peripheral fractures after adjustment for sex, age, BMI and BMD.

Paper III:

i) To explore the determinants of TBS and prevalent vertebral fractures on VFA.

ii) To explore whether prevalent vertebral fractures are determinants of TBS.

iii) To explore whether TBS is a determinant of vertebral fractures in a cohort of women with fragility fractures.

3 Materials and methods

3.1 Study population

3.1.1 The Norwegian Capture the Fracture Initiative - NoFRACT

The Norwegian Capture the Fracture Initiative (NoFRACT) was initiated at seven Norwegian hospitals from May 2015 (Fig. 2.). The aim was to assess the effectiveness of an intervention in terms of introducing a standardized program for assessment and treatment of bone fragility in fracture patients (120). To investigate the effect of the program, the rate of subsequent fracture (per 10 000 patient-years) from national register data in the intervention period (2015-2019) will be compared to the fracture rate before the intervention (2008-2015). Each of the seven hospitals will function as their own controls. Since data will be retrieved from national registers, the analyses will include all patients regardless of exposure to the intervention (intention to treat). By January 2019, 34,976 patients were enrolled in the study.

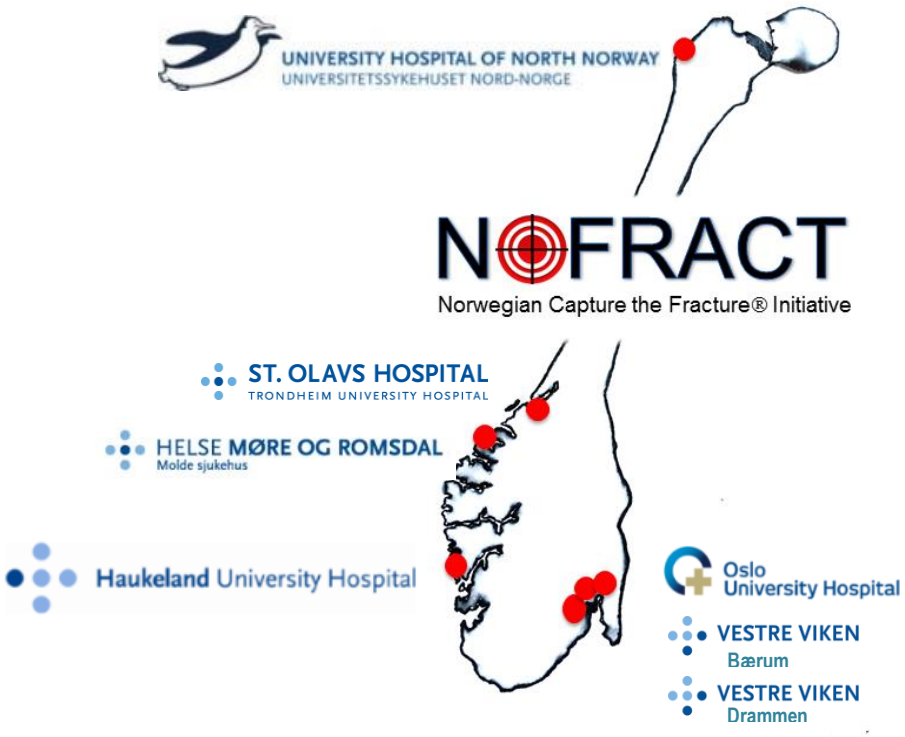


Fig. 2. Hospitals participating in the NoFRACT study across regions of Norway.

3.1.2 The sub-study of Norwegian Capture the Fracture Initiative

This consent based sub-study of NoFRACT was conducted at Drammen Hospital from 1 Jan 2016 to 31 Dec 2017 and at the University Hospital of North Norway, Tromsø from 1 Oct 2015 to 31 Dec 2017 (Fig. 3). Of all patients aged 50 years and above, attending these hospitals with a fragility fracture, more than 90% (n = 2682) were identified and offered fracture risk assessment (Fig. 4). For elderly in-patients with fractures of hip, vertebrae, two or more fragility fractures, or 10-year probability of MOF ≥ 20% using FRAX, the treatment decision was often made without using DXA (n = 1235). The participants were recruited among those who were referred to DXA (n = 1447), of whom 839 consented to participate in the study, 675 women and 164 men. Of 839 patients (530 in Drammen and 309 in Tromsø), 696 completed a questionnaire. Inclusion and exclusion criteria for the sub-study are shown in Table 1.

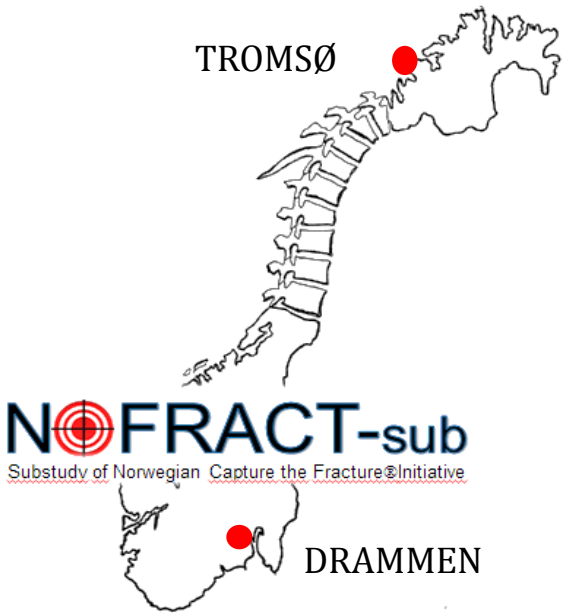


Fig. 3. Hospitals participating in the NoFRACT sub-study.

Inclusion criteria	Exclusion criteria
≥ 50 years of age Recent fragility fracture Competent to give consent	Fracture of fingers, toes, face or skull Difficulties with communication Cognitive dysfunction Short life expectancy

Table 1 Inclusion and exclusion criteria for the sub-study of NoFRACT.

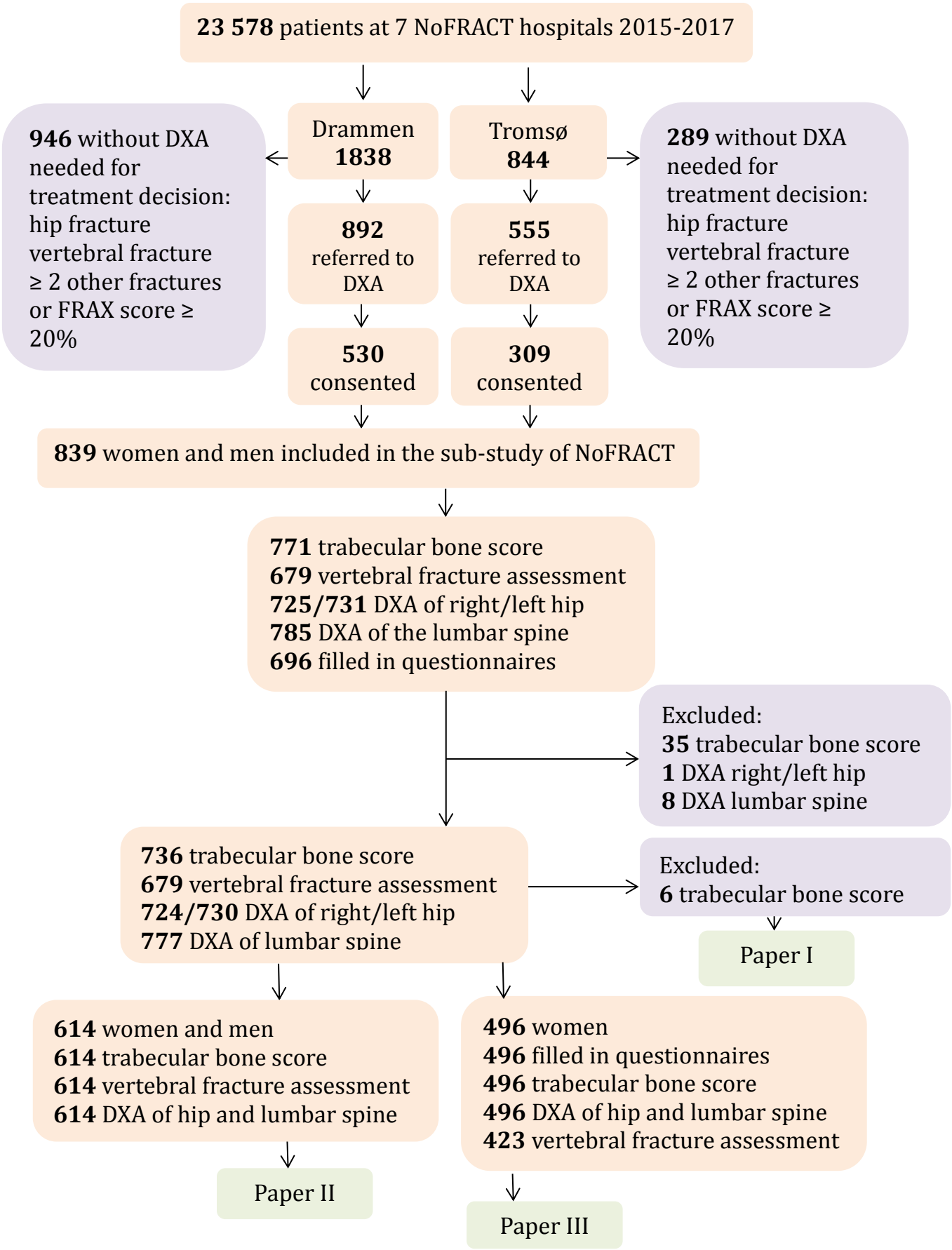


Fig. 4: Flow-chart for the participants in the sub-study of NoFRACT.

Of the 771 patients who had TBS calculated, 41 of these were excluded in paper I and 35 were excluded in paper II. Twenty-six patients were excluded due to BMI > 37 kg/m^2 (TBS values are not recommended for use in patients with BMI > 37 kg/m^2 because of the influence of soft tissue) and 15 patients were excluded due to fractures or anatomical aberrations in two or more vertebrae in paper I which did not give TBS result of L1-L4. In paper II, reanalysis of the TBS in six patients who did not have TBS calculated initially, lead exclusion of only 9 patients due to this. Unfortunately, this is wrongly explained in the method of paper II. Further, 679 of the patients had a lateral thoracolumbar scan performed for VFA.

Of the 725/731 patients with DXA scan of right/left hip, one patient was excluded because of poor image quality of the DXA scans, resulting in 777 patients with valid BMD measurement of at least one hip. Of the 785 patients with a DXA scan of the lumbar spine, 8 patients were excluded because of less than two evaluable vertebrae, hence 777 patients had valid BMD measurement of the lumbar spine. Exclusion of six more patients due to TBS (as described above) explained that 608 patients had valid values for both DXA and TBS and with VFA performed in paper I and 614 patients in paper II. Hence, 724/730 patients with DXA scans of the right/left hip, 777 with DXA of the lumbar spine, 679 with VFA and 730 with TBS calculated were included in the analyses of Paper I. The proportion of vertebrae that could not be assessed due to low imaging quality was 8.4%. They were mainly located in the upper thoracic region (Th4-Th6). No patients were excluded due to conditions known to affect bone metabolism, such as chronic kidney disease, use of AOD, hormone replacement therapy (HRT) or premenopausal status.

3.2 Ethics

All patients in the sub-study provided written informed consent and they were informed about the opportunity to withdraw the consent at any time. The study was approved by The Regional Committee for Medical and Health Research Ethics (REK 2014/2260) and was conducted in accordance with the World Medical Association Declaration of Helsinki. The NoFRACT main study (NCT02536898) and the sub-study (NCT02608801) were both registered separately in ClinicalTrials.gov. Data security was ensured by using a research platform for sensitive data at the University of Oslo.

3.3 Design

The NoFRACT sub-study was designed as a prospective observational study, with clinical examination and questionnaire at baseline, telephone interview, questionnaire and measurement of bone turnover markers (BTM) at 1-year follow-up and clinical examination, questionnaire and BTM at 2-year follow-up. All three papers in this thesis used baseline data on fracture patients with a cross-sectional design; with no fracture-free control group or follow-up.

3.4 Data from questionnaires

The participants answered a self-administered questionnaire at the time of inclusion concerning: years of age, ethnicity, number and site of fractures after the age of 50 years, parental history of hip fracture, type of comorbidity, medication and supplementation of calcium and vitamin D, number of falls the last 12 months, height loss, need of walking aids, frequency and duration of exercise, number of daily units dairy products, alcohol intake, current smoking, working status, home situation, self-reported health status and health related quality of life (EQ-5D). Men were asked about treatment for prostate cancer. Women were asked about use of HRT at menopause, current or previous use of aromatase inhibitors, postmenopausal status, number of children born and total number of months of breastfeeding (Appendix).

Exercise was reported as mean frequency of exercise per week (mean): never (0 times/week), 1 time/week (1 time/week), 2-3 times/week (2.5 times/week) and 4-7 times/week (5.5 times/week). Additionally the duration of each workout (mean) was reported: < 15 minutes (7.5 minutes), 15-29 minutes (22.5 minutes), 30-60 minutes (45 minutes) and > 60 minutes (75 minutes). Based on this information, we estimated hours of exercise as mean exercise time/week x mean minutes/workout. Consumption of dairy products was reported in unit dairy products per day (mean): 0 = none, 1-2 units/day (1.5 units per day), 3-4 units per day (3.5 units/day) and ≥ 5 units/day (6 units/day).

The study nurse registered additional clinical data at baseline: site and date of index fracture, date of baseline visit, use and type of AOD, calcium and vitamin D supplementation at baseline, type of AOD, calcium and vitamin D supplementation started after assessment, 10-year risk of hip fracture, MOF and osteoporotic fracture estimates calculated by FRAX and Garvan nomogram.

3.5 Bone mineral density

Height (m) and weight (kg) were measured in light clothing without shoes before BMD measurement. BMI was calculated as weight per square meter height (kg/m^2).

BMD was measured at the femoral neck and total hip at both sides and at lumbar spine (L1-L4), using iDXA Pro in Drammen (Fig. 5A) and DXA Prodigy Pro in Tromsø (Fig. 5B) (both GE Lunar, Madison, WI, USA). Phantom Quality Assurance (QA) of the DXA equipment was performed daily.

A

B

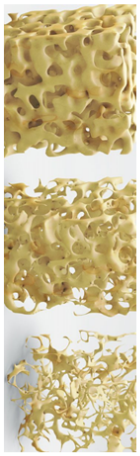
Fig. 5. Dual energy x-ray absorptiometry devices used for measurement of bone mineral density. IDXA Pro (A) and DXA Prodigy Pro (B).

The patients were positioned lying straight on the back in the center of the table (Fig. 6). The scan extended from the lowest vertebrae with ribs to the pelvic brim including all the vertebrae in total from L1 to L4. The hips were positioned with the femora straight on the table, parallel to the edge on the DXA image. The femora were rotated 15-25° inwards, achieved by using a position device placed between the ankles.

Fig. 6. Positioning of patient for BMD measurements of femoral neck, total hip and lumbar spine.

All fractured lumbar vertebrae were excluded. BMD T-scores were calculated using NHANES III reference population of female Caucasians aged 20–29 years for femoral neck and total hip (5) and Lunar female reference database for lumbar spine in both women and men, as recommended by ISCD (59).

The patients were categorized into those with normal BMD, osteopenia or osteoporosis at femoral neck or at the site with the lowest BMD T-score using the WHO classification (Table 2) (121):



BMD cathegory	BMD T-score
Normal	≥ -1
Osteopenia	<-1 and >-2.5
Osteoporosis	≤ -2.5

Table 2 WHO diagnostic categorization of osteoporosis based on bone mineral density (BMD) T-score.

3.6 Trabecular bone score

TBS was analyzed using TBS iNsight software (Medimaps, Geneva, Switzerland) Version 3.0.1 with processing of the DXA image of L1-L4. Standard mode was used. Fractured vertebrae were excluded. Patients with BMI below 15 kg/m^2 or above 37 kg/m^2 were excluded because of the influence of soft tissue, as recommended by MediMaps (122). TBS was analyzed directly after DXA scanning of the participants from Drammen, and after admission to a temporary license from MediMaps for images of the Tromsø participants. The European reference population was used for women and men.

TBS values were divided into 3 categories according to risk of major osteoporotic fracture: ≥ 1.310: low risk of fracture, between 1.230 and 1.310 medium risk for fracture and ≤ 1.230 high risk of fracture. This division is recommended in the TBS manual, and it is based on results from a meta-analysis of 14 population-based studies (Table 3) (103).

TBS cathegory	TBS value	Microarchitecture	Fracture risk
High	≥ 1.310	Normal	Low
Inter median	1.231-1.309	Partly degraded	Medium
Low	≤ 1.230	Degraded	High

Table 3 Trabecular bone score (TBS) values with associated microarchitecture degradation and fracture risk.

3.7 Vertebral fracture assessment

Images of the lateral thoracolumbar spine (T4-L4) were obtained using DXA scanner with the patient in a lateral decubitus position with flexed hips and lumbar support (Fig. 7). In patients who were not able to lie on the left side for instance due to fractures of the humerus or hip, reverse lateral scanning was performed (Fig 8).

Fig. 7. Positioning of patient for imaging of lateral thoracolumbar spine.

Fig. 8. Positioning of patient for reverse imaging of lateral thoracolumbar spine.

VFA was performed by TT Borgen utilizing the semiquantitative (SQ) vertebral deformity method of scoring by Genant et al. (123). This method combines the visual detection of deformed vertebrae in the Th4-L4 scan (Fig. 9A) with quantification of the deformity of the affected vertebrae. We also used the Encore DXA software built-in quantification tool, by manually labelling six points on the affected vertebrae; at the upper and lower edge of the posterior margin, centrally at the upper and lower endplate and at the upper and lower edge of the anterior margin (Fig. 9B). Percentage of height difference between the anterior and posterior (AP), anterior and middle endplate (AM) and posterior and middle endplate (PM) was calculated (Fig. 9C) and the site with largest height loss was chosen.

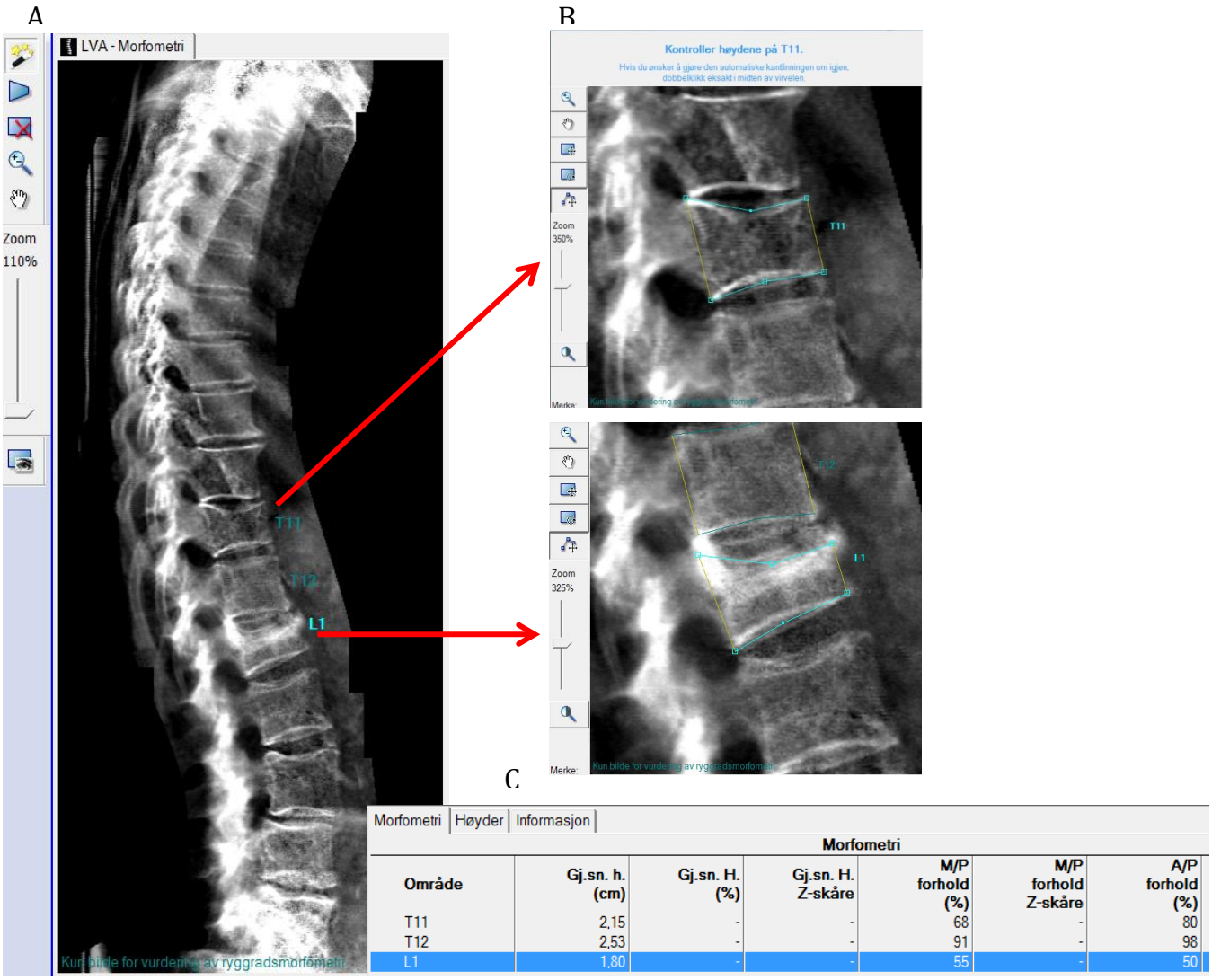


Fig. 9. Vertebral fracture assessment A) Lateral scan of thoracolumbar spine, B) six point labelling of deformed vertebrae and C) report of percentage height differences.

Deformity of fractured vertebrae was categorized into semiquantitative (SQ) grade 1-3 depending on percentage of height loss (Table 4). One or more SQ1, SQ2 or SQ3 fracture was called SQ1-SQ3 fracture and one or more SQ2 or SQ3 fracture called SQ2-SQ3 fracture. Presence of at least one SQ3 fracture was regarded as a sign of severe deteriorated microarchitecture in trabecular bone (124).

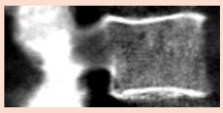
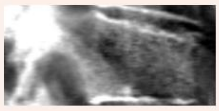
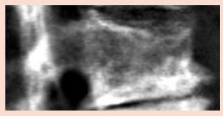
	Deformity grade	Fracture	Height loss
	SQ0	Normal	< 20%
	SQ1	Mild	20-25%
	SQ2	Moderat	25-40%
	SQ3	Severe	≥ 40%

Table 4 Quantification of deformity of fractured vertebrae. SQ = semi-quantitative.

Each lateral image was carefully investigated for other deformities that could explain height loss of vertebrae, such as Schmorl's impressions of the end plates, Modic lesions, and extensive degenerative changes with deformation, short vertebral height and physiological wedging of vertebrae, which were not counted as fractures.

In order to enhance the credibility of the VFA results, 200 lateral scans (150 scans from iDXA and 50 scans from DXA Prodigy Pro) were assessed independently by the study-nurse May-Britt Stenbro, who also is an ISCD certificated clinical technician with more than 4 year experience in performing and assessing lateral scans. She was blinded to the initial results assessed by TT Borgen. The inter-observer agreement of SQ1-SQ3 fractures between the clinicians showed a κ of 0.84 (95% confidence interval (CI): 0.70, 0.98), corresponding to an almost perfect agreement (125).

3.5 Statistical analyses

Paper I, II and III:

All the statistical analyses were performed utilizing Stata (Version 15, StataCorp LP, TX, USA). Continuous variables were calculated as mean ± SD and checked for normality by quantile-quantile (QQ) plot. Categorical variables were calculated as number with percentages (%).

Paper I:

Differences in means between the groups were calculated by using Student's t-test. The groups were compared using Fisher's exact test for small samples and chi square test in samples of more than 100. The inter-observer agreement of the assessment of SQ1-SQ3 fractures was calculated using Cohen's Kappa value (κ) with quadratic weighting. The inter-observer agreement by grade of severity of the fractures, within each SQ group, was calculated using Cohen's κ without weighting. We used Landis and Koch guidelines to interpret the levels of agreement of Cohen's κ: almost perfect agreement (κ > 0.81), substantial agreement (κ = 0.61 – 0.80), moderate agreement (0.41 – 0.60), fair agreement (0.21 – 0.40), slight agreement (0 – 0.20) and poor agreement (< 0) (125).

Paper II:

To explore differences in continuous variables between patients with different types of fractures, we used multiple linear regression analyses and adjusted for age and sex. The hip fracture group was chosen as reference group since this fracture type is considered as the most serious. The other fracture groups were compared to this reference group. Differences between subjects with central versus peripheral fractures and axial versus appendicular fractures were assessed for continuous variables using linear regression analyses and for

dichotomous variables using Fisher's exact test or Pearson Chi-squared test. These comparisons of risk factors between the fracture groups were presented in three models; unadjusted, adjusted for sex, femoral neck BMD and BMI, and after additionally adjustment for age. Sensitivity analyses were also performed, where subjects with central fractures were compared to those with forearm fractures, those with central fractures were compared to those with peripheral fractures ("other fractures" excluded) and central (vertebral fractures excluded) compared to peripheral fractures, which was shown in supplementary tables (online). The analyses of central versus peripheral fractures were performed in women and men separately to investigate whether there were differences between the sexes. Area under the Receiver Operating Characteristic curve (AUC) analyses were also performed to explore which bone phenotype that best was discriminating between subjects with central versus peripheral fractures.

Paper III:

We performed univariable linear regression analyses to investigate association between TBS (the outcome variable) and clinical relevant determinants (exposure variables): age, BMI, prior fractures after 50 years of age, falls within the last 12 months, parental history of hip fracture, comorbidities, use of medications, childbirths, breastfeeding, daily alcohol consumption, current smoking, exercise, intake of dairy products, SQ1-SQ3 fractures, femoral neck BMD and lumbar spine BMD. Only the determinants with p-level < 0.10 were retained and included further in the multivariable regression analyses. Because of potential multi-collinearity between femoral neck BMD, lumbar spine BMD and TBS, we tested different models for each of the traits to investigate the attribute in variance for each of the outcome variables that was explained by each of the introduced determinants. Non-significant determinants were omitted until only the exposure variables with statistical significant association ($p < 0.05$) remained. The removed determinants were reintroduced one at the

time to re-check for significance. The results were presented as β coefficients with 95% CI, the p-values, and explained variance (R^2).

Further, we performed univariable logistic regression analyses to explore associations between the outcome variable SQ1-SQ3 fractures (yes vs. no) and the determinants formerly used in the linear regression models (please see previous section). Only the determinants with p-level < 0.10 were retained and included further in the multivariable logistic regression analyses. Different models with and without TBS, femoral neck BMD and lumbar spine BMD as determinants were tested to explore the association with SQ1-SQ3 fractures. The non-significant determinants were removed one at a time until only the exposure variables with significant association ($p < 0.05$) remained. The removed variables were reintroduced to re-check for significance. The results were presented as odds ratio (OR) with corresponding 95% CI. The predictive accuracy of these models was assessed by calibration and discrimination. Hosmer and Lemeshow goodness-of-fit test was used to evaluate the calibration. The fit of the model was acceptable if the result was non-significant statistically in this goodness-of-fit test ($p > 0.05$). Discrimination of the SQ1-SQ3 fractures was assessed by analysis of AUC. Acceptable discriminatory capability was defined as an AUC > 0.7. We used standardized regression coefficients ($\beta_{\text{per SD}}$) and odds ratio ($OR_{\text{per SD}}$) with 95% CI to facilitate the comparison of the strength of the associations of each of the exposure variables with the outcome variables.

4 Main results

Paper I

High prevalence of vertebral fractures and low trabecular bone score in patients with fragility fractures: A cross-sectional sub-study of NoFRACT

VFA revealed vertebral fractures in 34.8% of the patients with fragility fractures and 34.0% had low TBS (≤ 1.23). In women and men, 190 of 549(34.6%), and 46 of 129 (35.7%) had vertebral fractures, and 206 of 590 (34.9%), and 42 of 133 (30.0%) had low TBS, respectively. In all patients with valid measures of both VFA and TBS, 53.8% had vertebral fractures, low TBS, or both (Fig. 10). In the patients with osteopenia at the femoral neck, 53.6% had vertebral fractures, low TBS, or both. Femoral neck BMD T-score ≤ −2.5 was found in 13.8% of all patients, whereas the corresponding figure was 27.4% using the skeletal site with lowest BMD T-score. Women exhibited lower BMD at all sites and lower TBS than men. Patients with prevalent vertebral fractures were older, exhibited lower BMD at all sites and lower TBS than those without vertebral fractures. Before assessment, 8.2% were taking AOD, and after assessment, the prescription rate increased to 56.2%, emphasizing the importance of risk assessment after a fragility fracture.

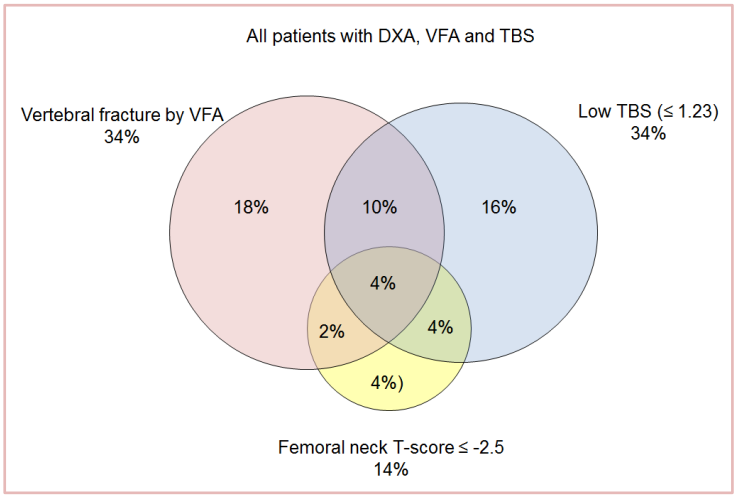


Fig. 10. Proportion of the patients with vertebral fractures, low TBS and osteoporosis of the femoral neck.

Paper II

Post-Fracture Risk Assessment: Target the Centrally Sited Fractures First! A Sub-Study of NoFRACT

We explored the potential differences between subjects with central (vertebral, hip, proximal humerus, pelvis) and peripheral (forearm, ankle, other) fractures. Patients with central fractures exhibited lower BMD of the femoral neck, total hip, and lumbar spine; lower mean TBS; and a higher proportion of SQ1-SQ3 fractures, SQ2–SQ3 fractures, and SQ3 fractures than patients with peripheral fractures. All analyses were adjusted for sex, age, and BMI; and the analyses of TBS and SQ1–SQ3 fracture prevalence was additionally adjusted for BMD. This suggests that patients with central fragility fractures exhibit more severe deterioration of bone structure, translating into a higher risk of subsequent fragility fractures. Hence these patients should get the highest priority in secondary fracture prevention, although attention to peripheral fractures should still not be reduced.

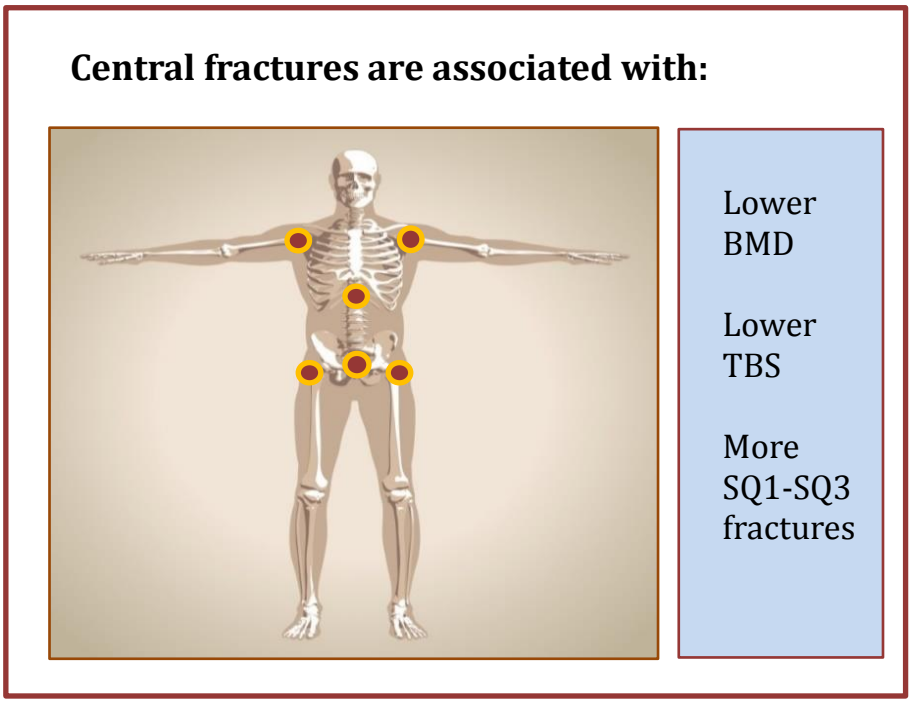


Fig. 11. Graphical abstract of paper II.

Paper III

Determinants of trabecular bone score and vertebral fractures in women with fragility fractures. A sub-study of NoFRACT

We explored the determinants of TBS and SQ1-SQ3 fractures and the associations between TBS and SQ1-SQ3 fractures in 496 women aged ≥ 50 years with fragility fractures. In multiple variable linear regression analysis, higher age, parental hip fracture and daily alcohol intake were associated with lower TBS (Fig. 12). Higher BMD of femoral neck and lumbar spine were associated with higher TBS. In multivariable logistic regression analyses, age and a history of prior fragility fractures were positively associated with SQ1-SQ3 fractures, while lumbar spine BMD was negatively associated with SQ1-SQ3 fractures. No association between TBS and SQ1-SQ3 fractures was found. Since TBS was not associated with SQ1-SQ3 fractures, we suggest they may act as independent risk factors, justifying the use of both in post-fracture risk assessment.

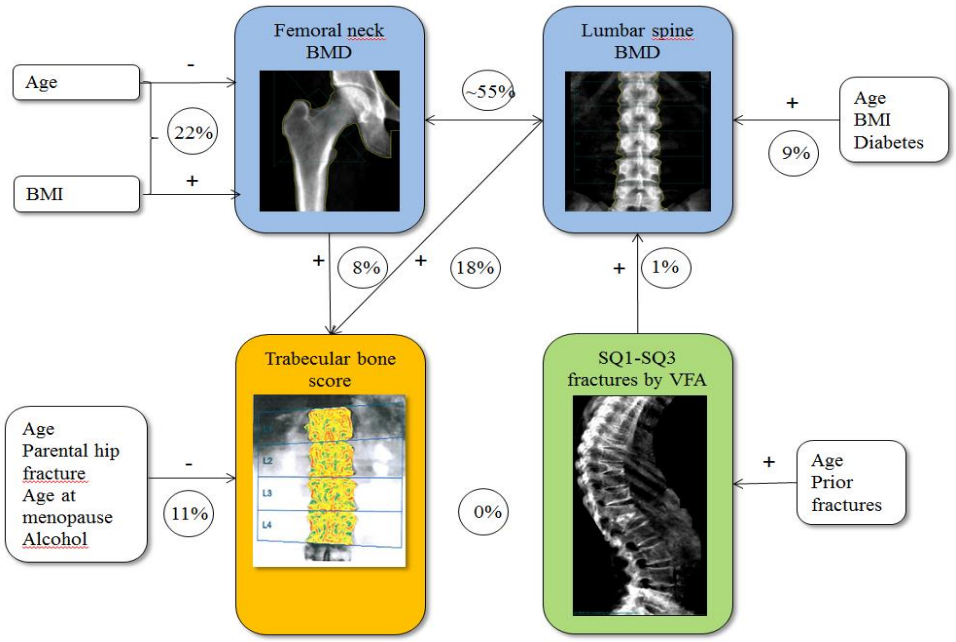


Fig. 12. Associations between trabecular bone score, vertebral fractures on VFA (SQ1-SQ3) and bone mineral density (BMD) at femoral neck and lumbar spine with the attributed variance of determinants. BMI = body mass index.

5 Discussion of main findings

5.1 Prevalence of vertebral fractures and low trabecular bone score in patients with fragility fractures

In this cohort of Norwegian women and men with recent fragility fractures about one in four patients had osteoporosis and more than half of the patients had osteopenia. One in three had low TBS, one in three had SQ1-SQ3 fractures, and more than half had either low TBS, SQ1-SQ3 fractures or both, even in patients with osteopenia. Women had lower mean femoral neck, total hip and lumbar spine BMD and TBS than men, while the proportion with SQ1-SQ3 fractures was equal in both sexes. Patients with SQ1-SQ3 fractures were older, exhibited lower BMD at all sites and lower TBS than those without SQ1-SQ3 fractures. After assessment, the prescription of AOD increased seven times, highlighting the need of risk assessment in these patients.

Of clinical interest is the large proporortion of patients with low TBS and SQ1-SQ3 fractures in patients with osteopenia, which most likely due to the inclusion of only patients with fragility fractures. These patients have increased risk of fractures, and stress the importance of AOD treatment in many of these, also in the absence of osteoporosis. Treatment recommendations are country spesific, due to markedly different fracture risk, cost/benefit and reimbursement in different countries (25). According to European and American guidelines, treatment should be considered following a fragility fracture. In NoFRACT, the treatment criteria were hip, vertebral, 2 or more fragility fractures, BMD T-score ≤ -1.5 and/or high FRAX score ≥ 20%, which lead to the increase in AOD prescription from 8% to 56%. TBS was not included in the criteria used for treatment initiation. Other FLS studies have shown similar increase in prescription rate from 5-19% before to 51-73% after assessment (126, 127).

As far as we know, this is the first study of both TBS and VFA in addition to BMD and clinical risk factors in Scandinavian patients with fragility fractures. The Scandinavian population has a higher rate of fragility fractures and osteoporosis than those of other ethnicities, and therefore studies on our population are of interest. Secondly, visualizing the amount of patients at high risk of fractures with TBS and VFA that are not captured by the BMD osteoporosis criteria provides important knowledge to the area of post-fracture risk assessment.

5.2 Targeting patients for post-fracture risk assessment

In patients with different types of fragility fractures, BMD at the femoral neck, total hip, and the site with lowest T-score was higher in patients with proximal humerus, forearm, ankle, and the group of "other fractures" than those with hip fractures. Mean TBS was higher in patients with "other fractures" than those with hip fracture. Further, we explored the differences between central and peripheral fractures and found that patients with central fractures had lower BMD, lower TBS and a higher proportion of SQ1–SQ3, SQ2–SQ3, and SQ3 fractures than patients with peripheral fractures. These results remained significant after adjustment for sex, age, BMI and BMD. The difference in TBS and SQ1-SQ3 fractures and SQ2-SQ3 fractures between patients with central and peripheral fractures was no longer significant after exclusion of patients with vertebral index fracture. The small number of patients in the group with central fractures might also play a role here. However, the differences in BMD and SQ3 fractures were still present.

We proposed grouping fracture patients into high risk and low risk groups according to the site of fragility fracture as an attempt to find a strategy to prioritize these patients timely to post-fracture risk assessment in the daily clinical work-flow. This grouping of patients arose from a clinical observation, that patients with central fractures (fractures of the hip, vertebrae, proximal humerus and pelvis) often presented lower BMD, lower TBS and more often had

SQ1-SQ3 fractures than patients with peripheral fractures (fractures of the forearm, ankle and other localizations). This difference was confirmed by the analyses.

Our suggestion that the central fractures are important to prioritize, is supported by recent results from the Tromsø Study, where hip and proximal non-hip non-vertebral (NHNV) fractures were associated with an increased risk in mortality of 105% and 49%, respectively, in women and 149% and 81%, respectively, in men (27). The distal NHNV fractures were not associated with increased mortality risk. Subsequent fractures, following any type of fracture, were associated with an increased risk of mortality of 89% in women and 77% in men. The mortality risk was highest in subsequent fractures following hip or proximal NHNV fractures.

Furthermore, centrally sited fractures were associated with a higher risk for subsequent fractures in a study of more than 350 000 American women investigated through Medicare data (81). In this study, vertebral, pelvic, clavicle and humerus fractures exhibited the highest rate of subsequent fractures, whereas crus and ankle fractures had the lowest rate. After 1, 2 and 5 years, the all over risk of subsequent fracture was 10, 18 and 31%; the risk following a vertebral fracture was 14, 26 and 40%, and the risk following a crus fracture was 7, 12 and 19%, respectively. They also demonstrated an increased mortality rate at 1,2 and 5 years following a hip fracture of 19, 31 and 64%, and following a clinical vertebral fracture 14, 24 and 54%, respectively. This also supports that patients with central fractures are important to target.

Recently, Kinnard et al. from the Hospital of Brugmann, Brussels, Belgium, wrote a Letter to the Editor of Journal of Bone and Mineral Research, which is not yet published. They had found our reclassification of fractures interesting, and had applied it to their data from the population-based FRISBEE cohort of 3560 patients with 754 osteoporotic fractures followed for 58 months (range 0.1-135). They also included fractures of sternum, ribs, scapula and clavicles in the

group of central fractures. In Cox model analyses they calculated hazard ratio (HR) of a subsequent fracture after a MOF or a central fracture. All the results were adjusted for age, BMD and BMI. They found that HR for any fracture, vertebral fracture and a central fracture was 1.72, 2.63 and 2.75 after a central fracture, respectively (all $p < 0.05$). MOF did not predict subsequent fracture significantly, which might be due to "dilution" of the risk by the forearm fractures, which are categorized as a MOF, but in our analyses showed higher TBS, lower proportion of SQ1-SQ3 fractures and higher BMD than the central fractures. Hip fractures did not predict subsequent fractures in this cohort, maybe because of small number of patients (n = 24). These results support our assumptions that patients with central fractures have a higher risk of subsequent fractures. Kinnard et al. suggested that "central fractures appear to be more predictive of further fractures than MOFs, which strengthen the interest of a new classification proposed by Borgen et al."

We have suggested a new model to prioritize patients with fragility fractures for post-fracture risk assessment. Since FLS is becoming a world-wide concept, models to approach the large amount of patients, are of interest. Although it is more or less obvious that patients with central fractures have lower BMD, lower TBS and a higher proportion of SQ1-SQ3 fractures than patients with peripheral fractures, also after adjustment with age, showing and quantifying this is novel.

5.3 Determinants of trabecular bone score and prevalent vertebral fractures in women with fragility fractures

The determinants of TBS and SQ1-SQ3 fractures were studied in women with fragility fractures. Higher age, parental hip fracture and daily alcohol intake were associated with lower TBS, whereas higher femoral neck BMD and lumbar spine BMD were associated with higher TBS. Higher age and a history of prior fragility fractures were positively associated with SQ1-SQ3 fractures, whereas lumbar spine BMD was negatively associated with SQ1-SQ3 fractures. SQ1-SQ3

fractures were not determinants of TBS and TBS was not a determinant of vertebral fractures in this cohort of women with fragility fractures.

We expected to find an association between TBS and SQ1-SQ3 fractures, since TBS is a textural index of bone structure measured in the lumbar vertebrae and all vertebrae consist largely of trabecular bone. There has previously been found an association between TBS and SQ1-SQ3 fractures in studies of elderly French and Japanese women (105, 128), but not in the studies of elderly Swedish women (129) or in men in the MrOs and Manitoba study (104, 130). Why these findings diverge between studies is not clear, but several factors may be of importance. Firstly, genetic factors seem to explain much of the variation in TBS and vertebral fractures. Genetic factors may vary considerably between the countries and the cohorts. Scandinavian women are a genetically homogenous group, with the highest prevalence of vertebral fractures in Europe (31). Studies on genetics also show that vertebral fractures are not necessarily linked to BMD. As an example, GWAS has identified a locus on chromosome 2q13 that is associated with clinical vertebral fractures in women, independently of BMD (73). Some studies have also shown an association between vertebral fractures and BMD, but with a weaker association, and the genetics behind vertebral fractures are complex. Since TBS correlate with BMD, genetics might be an explanation why we did not find any association between TBS and SQ1-SQ3 fractures in our cohort. Secondly, TBS is calculated from the lumbar spine BMD images. In our cohort, BMD of the lumbar spine was the single most important determinant of TBS and explained 18% of the variance, while 8% of the variance in TBS was explained by femoral neck BMD. SQ1-SQ3 fractures were only weakly negatively associated with lumbar spine BMD (explained 1% of the variance in lumbar spine BMD) and we did not find any association between SQ1-SQ3 fractures and BMD at the femoral neck. We suppose, that in this cohort of women with fragility fractures, the SQ1-SQ3 fractures gives information of reduced bone strength that is not reflected by BMD nor TBS.

We found an explained variance of TBS by femoral neck and lumbar spine BMD of 26% and 35%, respectively, in unadjusted Pearssons correlation tests, and 8% and 18%, respectively in adjusted models. This was higher than the explained variance by femoral neck and lumbar spine BMD in the women in the Manitoba Study which was 7% and 11% unadjusted, respectively, and 4% and 9% in adjusted models, respectively (102). The reason might be that all the NoFRACT women had sustained clinical fragility fractures, compared to only 14% of the women in the Manitoba cohort. In addition, we excluded all patients with BMI > 37 kg/m^2, which was not done in the Manitoba study. In patients with higher BMI than 37 kg/m^2, TBS becomes false low. This might have diluted the association between BMD and TBS in the Manitoba study. In paper III, unfortunately this is wrongly referred in the third section in the discussion. The the total explained variance of TBS (20% after adjustment for femoral neck BMD and 28% after adjustement for lumbar spine BMD) was compared to the unadjusted correlation coeffecient (R^2) in the Manitoba study. We have informed Osteoporosis International about this, and hope this can be corrected before the paper is printed. However, explained variance of TBS by BMD was markedly higher in the NoFRACT study compared to the Manitoba Study.

Drawing lines to paper I, only about one third of the patients with low TBS or SQ1-SQ3 fractures had both features present at the same time, suggesting that these might capture different aspects of bone strength. Since lumbar spine BMD attributed the single most important variance in TBS, this may infer that TBS reflect some of the same bone properties as BMD, connected to quantity of mineralized bone (amount or distribution of mineralized bone). Since there were only a weak association between SQ1-SQ3 fractures and lumbar spine BMD, and no association with TBS, SQ1-SQ3 fractures might mirror more aspects of bone quality (131).

Studies on determinants of TBS have been done before, but to our knowledge not in women with fragility fractures.

6. Methodological considerations

6.1 Study design

The results presented in this thesis are based on a cross-sectional designed study and do not include a control group. The cross-sectional design was chosen from a time-perspective, since the follow-up data of the sub-study were not completed within the time limits of the ph.d grant. Since NoFRACT has a clinical approach to post-fracture risk assessment of a large volume of patients, we did not prioritize our resources to recruit a control group.

In this cross-sectional study, all the information was collected at the baseline visit, at a single point in time. This cross-sectional design is suitable for exploring prevalence of outcomes and determinants of health in a cohort (132). It allowed us to compare numerous variables at the same time. However, since the outcome and exposure variables were not followed over time, we could not study incidence, risk or causality. The results of a cross-sectional study must be interpreted after careful consideration of possible biases (please see next section).

We did not have a fracture-free control group, which could have provided us with the possibility to study causality. However, the case-control design is more appropriate in conditions with low prevalence, which is not the case of bone fragility and fractures in Norway.

In paper I-III, we described and compared the prevalence of clinical risk factors for fracture in subgroups of the cohort. The cross-sectional design was proper for this purpose, but the selection of patients in the cohort has to be considered when interpreting the findings (please see next section). Since we did not have a control group, the results in paper I were discussed in relation to findings in population-based and other FLS studies. In paper III, we explored the associations between TBS and SQ1-SQ3 fractures and risk factors for fracture.

The cross-sectional design was proper for exploring such associations, but could not be used for exploring causality.

6.2 Internal validity

Internal validity in a study denotes how well other possible explanations of the results of the study are ruled out. The internal validity of a study is considered appropriate if there are no essential systematic errors. There are three major types of systematic errors: Selection bias, information bias and confounding. These errors are not reduced by increasing the size of the cohort studied.

6.2.1 Selection bias

Selection bias can occur at the time of recruitment of subjects into a study. If the selection is not random, the study cohort will not be representative for the population that is intended to be analyzed. Common selection errors are connected to the origin of the patient population, the recruitment and willingness of the patients to participate. The selection bias must be taken into account when conclusions of studies are drawn.

In our study, all the participants were less healthy than the general population, since they all had sustained a fragility fracture. Of these, there was a selection of healthier patients to the sub-study. The elderly patients with a hip or vertebral fractures and high risk of subsequent fractures (FRAX > 20%) were often not referred to DXA and therefore not included in the sub-study (please see methods). In addition, many of the elderly or frail patients who were admitted to DXA were not competent for consent, hence not included. The cohort of the sub-study were younger, had a higher proportion of women and a lower proportion of patients with hip fracture than in the whole fracture cohort (Table 5 and 6). Due to lack of time of the study nurses and some of the patients, many

patients were never asked to consent and were not included in the sub-study. This was more random, since the consultation itself took the same time, regardless of age and fracture type and the intention was to include as many patients as possible if there was enough time.

The selection of healthier and younger fracture patients has probably skewed the results in a "healthier" direction. The prevalence of pathological features in the cohort is maybe underestimated and the associations between exposure and outcome variables (for instance the association between TBS and SQ1-SQ3 fractures) may be diluted compared to the whole fracture cohort.

The comparisons between women and men might also be skewed by a smaller proportion of women than men with hip fractures in percentage terms (7.3% vs. 14.6%), although a higher number of women than men had hip fracture in absolute terms (n = 49 vs. n = 24). Although this might indicate that the cohort of women was healthier than the men, the women still had lower BMD and TBS than men. The proportion of women participating in the sub-study was higher than the proportion of women with fractures registered in the quality assurance registers (Table 5 and 6). This might also lead to increased differences when comparing women and men.

The selection of patients into the sub-study should have reflected the whole fracture population, regarding proportion of fracture types, age and sex. This would, however, resulted in a smaller cohort, since the number of patients with hip fracture was relatively smaller. In the whole cohort, half of the patients had central fractures, whereas in the sub-study only one in four had central fractures. The differences between central and peripheral fractures might be larger if the group of central fractures had been representative.

	Quality assurance register Drammen	NoFRACT Sub-study Drammen	p-value
All, n	1838	530	
Women, n (%)	1388 (77.8)	344 (81.3)	**< 0.001**
Age, years (SD)	73.1 (10.1)	67.3 (8.8)	**< 0.001**
Hip fracture, n (%)	513 (27.9)	65 (12.3)	**< 0.001**
Vertebral fracture, n (%)	121 (6.6)	38 (7.2)	0.623
Humerus fracture, n (%)	254 (13.8)	72 (13.6)	0.943
Forearm fracture, n (%)	490 (26.7)	199 (37.6)	**< 0.001**
Ankle fracture, n (%)	190 (10.3)	94 (17.7)	**< 0.001**
Other fractures, n (%)	270 (14.7)	62 (11.7)	0.088

Table 5 Sex, age and type of index fractures in all patients in identified and in the patients included in the sub-study in Drammen from 2016-2018.

	Quality assurance register Tromsø	NoFRACT Sub-study Tromsø	p-value
All, n	260	309	
Women, n (%)	195 (76.6)	251 (81.2)	**< 0.001**
Age, years (SD)	69 (11)	64.1 (8.6)	**< 0.001**
Hip fracture, n (%)	55 (21)	8 (2.6)	**< 0.001**
Vertebral fracture, n (%)	5 (2)	12 (3.9)	0.291
Humerus fracture, n (%)	26 (10)	33 (10.7)	1.000
Forearm fracture, n (%)	75 (29)	110 (35.6)	0.106
Other fractures, n (%)	99 (38)	146 (47.2)	**< 0.001**

Table 6 Sex, age and type of index fractures in patients registrered in the quality assurance registry in Tromsø from October 2015 through August 2017 (133) and in the patients included in the sub-study in Tromsø from 2015-2018.

6.2.2. Information bias

Information bias can arise if there is error in the information collected from the study participants or in measured variables. This can be due to inadequate definition of the variables studied or to imperfect data collection procedures. Misclassification of the exposure or outcome status of the participants studied can lead to under- or overestimation of the associations between exposure and outcome variables. If the misclassification is non-differential, the groups of patients that are compared are equally affected, and that the error might dilute the association. If the misclassification is differential, the rate of misclassification differs between the groups, and can result in under- and overestimation of the estimated associations.

Data from questionnaire

Information collected through the self-administered questionnaires at inclusion, could be flawed due to recall bias, under- or over reporting. Many of the questions concerned events from the past, such as years since previous fractures, history of parental hip fracture, years since diagnose of certain diseases, years of medication, months of breast-feeding and age at menopause. In general, information of smoking and alcohol intake is often under-reported, and information of exercise often over-reported. One would expect that these errors would be similar distributed in the cohort, regardless of grouping in the analyses (women vs. men, patients with vertebral fractures vs. patients without vertebral fractures, central vs. peripheral) but might have given errors in the estimates of prevalence of these variables and thus diluted the results for the associations.

BMD

Height and weight were measured without shoes and in light clothing in all patients before BMD. Since there were two study sites, different measure devices for height and weight were used, and we did not compare these measure devices against each other. This could potentially serve as a systematic information error. On the other side, there were no differences in mean height and weight between the patients in Drammen and Tromsø (167.2 cm vs. 167.6 cm and 74.7 kg vs. 75.3 kg, both $p > 0.05$) and comparison of these two cohorts was not the objective of the study.

BMD was measured at two different GE Lunar DXA devices, iDXA Pro and Prodigy Pro which could lead to observation biases. Both DXA machines were brand new at the beginning of the study, and both machines had been calibrated against the same step-wedge aluminum phantom by the installer. Thereafter, daily quality assurance test of both machines have been performed with the same type of phantom (QA-block), though they were not 100% similar. Ideally, we should have cross-calibrated the two machines during the study period. However, there are several studies showing a correlation coefficient (R^2) of 0.98-0.99 when cross-calibrating iDXA and Prodigy devices (134, 135), so this difference might be less than the intra- and inter-observer variance. Positioning of the patients was standardized, and all the study nurses went through the same course in scanning technique training before the data collection started.

Mean BMD measured at the iDXA in Drammen vs. the Prodigy Pro in Tromsø of the femoral neck and total hip was 0.811 g/cm^2 vs. 0.824 g/cm^2 and 0.857 g/cm^2 vs. 0.880 g/cm^2 ($p = 0.194$ and 0.035). For lumbar spine the corresponding values were 1.068 vs. 1.038, respectively ($p = 0.053$). The tendency towards lower total hip BMD and higher lumbar spine BMD in patients from Drammen vs. Tromsø might be explained by higher age (65.9 years vs. 67.0 years, $p < 0.001$). After adjustment for age the differences in BMD were no longer significant ($p > 0.05$).

TBS

The same software was used for calculation of TBS at both centers. Calibration was performed at both DXA devices with 6 scans of the same phantom (3v). Standard mode was chosen for all patients. Systematic errors considering TBS should therefore be the same as discussed for lumbar spine BMD, as discussed in the previous section.

VFA

In 785 patients with DXA, only 679 had lateral scan of the thoracolumbar spine. Many patients were not able to lie on the left side, which is the standard position (Fig. 7), due to recent fracture (for instance fracture of the hip or humerus). After some time, reverse lateral scanning was introduced, and the patients could also be scanned laying on the right side (Fig. 8). Some lateral images were not performed due to lack of time, which was more random. Patients who did not have VFA performed had a higher proportion of hip fractures and a lower proportion of forearm fractures (Table 7). The numbers of patients with hip fractures who did not have VFA performed was relatively low (n=23), however this was 1/3 of the patients with hip fractures in the sub-study. On the other hand, the proportion of patients with forearm fractures who did not have VFA performed was lower. This has led to a lower proportion of VFA in the group of central fractures, and a higher proportion with VFA in the group of peripheral fractures, which might have diminished the statistical power when comparing central and peripheral fractures. Since many of the patients with hip fractures did not have VFA performed, the results of SQ1-SQ3 fractures in these patients might not be representative.

	VFA performed	VFA not performed	p-value
n	679	160	
Women, n (%)	550 (81.0)	125 (78.1)	0.835
Age, years (SD)	65.9 (8.6)	65.7 (9.6)	0.836
Hip fracture, n (%)	50 (7.4)	23 (14.4)	**0.008**
Vertebral fracture, n (%)	39 (5.7)	11 (6.9)	0.579
Humerus, n (%)	79 (11.6)	26 (16.3)	0.113
Forearm, n (%)	270 (39.8)	39 (24.4)	**< 0.001**
Ankle, n (%)	123 (18.1)	25 (15.6)	0.725
Other, n (%)	118 (17.4)	35 (22.5)	0.210
BMD femoral neck, g/cm^2 (SD)	0.815 (0.118)	0.818 (0.133)	0.820
BMD lumbar spine, g/cm^2 (SD)	1.058 (0.182)	1.062 (0.194)	0.830
TBS (SD)	1.27 (0.10)	1.27 (0.11)	0.728

Table 7 Sex, age, type of index fracture, bone mineral density (BMD) and trabecular bone score (TBS) in patients VFA performed and not.

The image quality of the lateral scans obtained by iDXA was considerable better than the images obtained by Prodigy Pro, mainly due to the three time higher radiation dose used. Vertebrae that had to be excluded due to poor imaging quality was 6.4% in images obtained by iDXA vs. 12.2% of images obtained by Prodigy. This might lead to an under-estimation of fractures in the cohort from Tromsø. Of the total number of vertebrae of the patients from Drammen and Tromsø, fractures were found in 5.0% and 3.7%, respectively, increasing to 5.4% and 4.2% after exclusion of non-evaluable vertebrae. The proportion of patients with SQ1-SQ3 fractures was 34.9% in Drammen and 34.4% in Tromsø. The proportion of SQ1, SQ2, SQ3 fractures in all fractured vertebrae in patients from Drammen vs. Tromsø were 43% vs. 49%, 35% vs. 46% and 22% vs 5%,

respectively. This infers that there might be an underestimation of fracture severity in images obtained by Prodigy, though younger patients in the cohort from Tromsø might also be an explanation. Adjustment for age was done in the analyses in Paper II and III which might have compensated for some of these differences.

We used the semiquantitative method of Genant to identify and classify the vertebral fractures. This method was chosen because we were familiar with it and the method is widely used and recommended by ISCD. There is an ongoing debate whether this method overestimates the prevalence of vertebral fractures, since many of the SQ1 fractures potentially can be deformations which are not fractures. Of all fractured vertebrae in our study, 45% were SQ1 fractures compared to 5% in the population-based Tromsø Study from 2007-2008 (30). The identification of so many mild fractures could be due to the use of new DXA equipment with improved image quality, particularly the iDXA. However, five of the 50 vertebral index fractures in our study diagnosed by x-ray, CT or MRI were *not* diagnosed as vertebral fracture according to Genant's semiquantitative method on VFA. There are other methods of VFA that are more sensitive and capture fractures with less height loss than 20%, which could have increased the number of patients with vertebral fractures.

We included SQ1 fractures in our definition of prevalent vertebral fractures (SQ1-SQ3 fractures), which potentially could lead to a misclassification of vertebral fractures. If so, this would be a non-differential misclassification, with all groups equally affected in paper I and II. In paper III, this potential misclassification could dilute the association between SQ1-SQ3 fractures and the fracture risk variables studied. However, we performed additional regression analyses included only the SQ2-SQ3 fractures and SQ3 fractures, and found no differences in the associations.

All VFA assessments were performed by the same health professional (TT Borgen) who followed the standardized method of Genant of classification of fractured vertebrae. Another assessor (M-B Stenbro), an experienced DXA technician, reviewed 200 of the VFA images. The inter-observer agreement was calculated. Kappa was calculated and the inter-observer agreement was considered as almost perfect.

Statistics

Paper I was the first publication with a descriptive focus. Although the patients were stratified according to sex and prevalent vertebral fractures, adjustment for relevant confounders such as age, BMI and BMD could have been performed. This was introduced in paper II and III, and the analyses used were recommended by biostatistician.

In paper I we experimentally calculated area under the receiver operating characteristic curve (AUC) for femoral neck BMD T-score, TBS L1-L4, VFA and combinations of these, with comparison of the standardized values to assess which test(s) had the best ability to discriminate between patients with and without prevalent vertebral, hip and forearm fractures. Initially we found this issue relevant, but after some time we understood that these analyses were not proper due to the cross-sectional design and the lack of a control group in the study.

In all patients with VFA we also calculated the semi quantitative spinal deformity index (SDI) as the sum of SQ deformity grade of all vertebras from Th4 to L4; SQ 0 = 0 points, SQ 1 = 1 point, SQ 2 = 2 points and SQ 3 = 3 points (136). We planned to use SDI as a continuous variable, but unfortunately this variable was far from normally distributed, and strongly left skewed. Despite numerous efforts, we were not able to transform SDI for use in parametric tests.

Therefore we categorized the vertebral fractures into SQ1-SQ2, SQ2-SQ3 and SQ3 fractures.

6.2.3 Confounding

Confounding is a phenomenon where an association between two variables changes when a third variable is introduced. Hence the confounding variable is associated with both the exposure and the outcome variables. The confounding variable is not the variable that is studied, but it can influence on the result and conclusion and the association between the exposure and outcome can be flawed. The confounding variable can strengthen, weaken, eliminate or introduce an association between the exposure and the outcome. Such effects can be corrected by adjustments for potential confounding variables. In paper II we adjusted for age, sex, BMI and femoral neck BMD, which are variables associated with bone properties. In paper III all significant variables from the univariable analyses were included in multivariable linear or logistic analysis; hence the remaining variables in the models were adjusted for the confounding variables. Variables with high correlation, such as femoral neck and lumbar spine BMD were not combined in the same model simultaneously.

6.3 External validity

External validity of a study is to which degree the results can be generalized to the whole population or other populations. We studied a cohort of women and men aged 50-91 years, mean age 65.8 years of whom 97% were Caucasian. All had sustained a recent fragility fracture.

The patients were recruited from Drammen in southern Norway and Tromsø in northern Norway. The Norwegian Epidemiological Osteoporosis Studies (NOREPOS) has previously shown lower femoral neck BMD in men and in

women > 60 years of age in the population in Bergen the south of Norway compared with the population in Tromsø in the north of Norway (137). This indicated a south-north gradient in femoral neck BMD which we did not find. However, we did find a lower total hip BMD and higher lumbar spine BMD in the participants from Drammen compared with the participants form Tromsø, but these differences vanished when adjusting for age ($p > 0.05$). No difference in fracture rate between southern and northern Norway has been demonstrated, but an increased fracture rate in urban vs. rural areas has been demonstrated (138). Both study sites recruited patients from their cities and the surrounding areas; the cohort is considered to be representative for patients from both urban and rural areas.

The cohort of this sub-study is not representative for the general Norwegian population, because of the selection of individuals with fragility fractures. Further it is not representative for all patients with fragility fractures, because of the healthy selection bias, as previously described. However, the cohort can be representative for Norwegian patients presenting in an osteoporosis clinic after a fragility fracture or captured by FLS and remitted to DXA, because patients with hip, vertebral and several fractures are often assessed without DXA. Since the Norwegian population has the same fracture rate as the Scandinavian population, we believe that our results might be applicable for Scandinavian FLS out-patients as well. Since the Scandinavian population has a higher fracture rate than other populations, the results are perhaps not applicable on other populations.

6.4 Strengths and limitations

The strengths of the study are the large sample size of the total cohort, the large number of clinical variables collected, the high clinical relevance, the inclusion of patients from two study sites and the high inter-observer reliability of VFA demonstrated.

In addition to the proposed selection biases and information biases, discussed in the previous sections, the lack of a control group and the cross-sectional design were limitations. Further, some of the sub-groups of fractures were small, particularly the number of men, and perhaps also the number of patients with hip fractures with VFA performed. Therefore some of the conclusions might not be applicable to these groups. The cohorts of women studied in paper III may have been too small to demonstrate associations between the outcome variables (SQ1-SQ3 fractures and TBS) and certain risk factors.

Bone measurements were only performed at central sites, which is also a limitation taking into account the large number of peripheral fractures. There are several prospective studies that have demonstrated that low BMD at central sites (54) and peripheral sites (52, 60), predict all types of fracture. However, a central measurement site predicts central fractures better, and the peripheral measurement site predicts peripheral fractures better(6).

7 Ethical considerations

All patients in this sub-study provided written informed consent and were informed that they could withdraw this at any time. The patients got the same diagnostic assessment and treatment regardless of the participation in the sub-study or not. The examinations did not pose any risk to the participants. DXA emits harmless doses of x-rays, and the blood sampling procedure comprises a needle prick.

The purpose of the FLS concept and NoFRACT is secondary fracture prevention by screening patients at high risk of having bone fragility, high risk of subsequent fractures and increased risk of death.

Systematic screening of fracture patients seems to be in accordance with the principles for screening stated by WHO (139):

- ☑ The condition that is screened for must be a substantial health problem
- ☑ An accepted treatment must be available
- ☑ It must be possible to diagnose the disease at an early stage
- ☑ The diagnostic tests and treatment must be available and acceptable for the patients
- ☑ The natural progression of the condition must be properly understood
- ☑ There must be a common understanding of who needs to be treated
- ☑ The costs by identifying and treat the patients must be reasonable compared to other use of the health resources.

In my opinion, all the screening criteria mentioned above can be justified in the NoFRACT study. Fragility fractures are a substantial health problem in Norway with high economical and personal costs. Well documented AOD are available to a reasonable cost, and diagnostic tests are available and acceptable for the patients. The progression of bone fragility is properly understood, the challenge is to get this knowledge out to the health professionals and patients. Through

NoFRACT, Norway has eventually got treatment recommendations for patients with fragility fractures, endorsed in the medical environment and adapted in clinical use at many hospitals. There is still one step left to get these recommendations into official Norwegian guidelines. Through NoFRACT, we have shown that screening of fracture patients can be introduced into hospital routines with small personal resources. To reduce the high fracture rates, economical and personal costs of fractures in Norway, screening of a high risk population is more cost-effective than screening in a low risk population.

The question is whether identification of individuals at high risk of new fractures is right. On the one hand, this is an absolute necessity if the health care system should be capable to meet the expected large "silver wave" of elderly with fragility fractures the next decades. On the other hand, is it right to uncover information about increased fracture risk if the patient could live happy without knowing?

The fundament of preventive medicine is to reduce the incidence of diseases with potential serious outcome. Bone fragility increases the risk of fractures with well documented high risk of morbidity and mortality (27). This justifies the FLS concept of the NoFRACT project. Many patients have expressed gratitude for eventually having their osteoporosis diagnosed after their second, third or fourth fracture. Very few patients express disappointment of getting the diagnosis, and refuse the recommended treatment. However, all patients who are assessed are informed about the results, their risk of subsequent fractures and the treatment options available. The patients decide themselves if they want to receive the proposed treatment or not and their autonomy is respected.

8 Conclusions

Since low TBS, vertebral fractures or both were present in more than half of women and men who were assessed after fragility fractures; we conclude that TBS and VFA seem to be important tools in post-fracture risk assessment, especially in patients without osteoporosis. TBS and VFA seem to capture different aspects of bone strengths, which are supported by our findings of no associations between TBS and SQ1-SQ3 fractures.

Capturing patients with fragility fractures for fracture risk assessment as recommended by IOF is meaningful and important, as shown in this study by a seven fold increase in prescription of AOD.

Patients with centrally sited fragility fractures have lower femoral neck BMD, lower TBS and higher prevalence of SQ1-SQ3 fractures than patients with peripherally sited fractures. We infer that the patients with central fractures exhibit more serious deterioration of bone structure and a higher risk of subsequent fractures. This is in line with findings of increased risk of subsequent fractures and mortality in patients with centrally sited fractures. We conclude that of all patients with fragility fractures, everyone should be assessed, but the patients with central fractures must be prioritized first.

Higher age, parents with a history of hip fracture and daily alcohol intake were associated with lower TBS, whereas higher lumbar spine BMD and femoral neck BMD were associated with higher TBS. Higher age and prior fractures were positively associated with SQ1-SQ3 fractures, whereas lumbar spine BMD was negatively associated with SQ1-SQ3 fractures. We found no association between TBS and SQ1-SQ3 fractures. We conclude that daily alcohol consumption and low BMD are modifiable risk factors, which are important to target in fracture prevention strategies, which is in line with general recommendations. Since TBS

and SQ1-SQ3 fractures were not associated, we believe that each of them acts as independent risk factors for fracture, and that both are important supplements to BMD in post-fracture risk assessment.

9 Implications and further research

This work has mainly had a clinical approach to post-fracture risk assessment, the characteristics of the patients, the work-flow and understanding of the connections between TBS, VFA and BMD. A next step is explore the predictive values of these tools, and compare them with scores from risk assessment tools, and search for the most precise and efficient way to assess fracture risk in patients after a fracture. Furthermore, recent studies show results that support a peripheral measure site of bone strength to better predict peripheral fractures. A multifactorial, holistic approach with high sensitivity and specificity is desirable, yet it should be as simple as possible for use in the clinic.

We have proposed a classification of central and peripheral fractures, which in prospective Belgian study has shown a higher predictive value of future fractures than MOF. If these findings can be confirmed in other prospective data, central fractures could maybe have a place in future fracture risk calculators, both as risk factor and outcome. This might identify the individuals with the highest risk of serious fractures and death more precisely.

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Reproduction of "The sun" by Edvard Munch

"Nature is not only all that is visible to the eye... it also includes the inner pictures of the soul"

Edvard Munch

Appendix

Løpenr.: ☐☐☐☐ ☐☐☐☐☐ **Personnr.:** ☐☐☐☐☐☐ ☐☐☐☐☐

Kjønn: ☐ K ☐ M **Dato utfylt:** ☐☐.☐☐.☐☐☐☐

Alder (år): ☐☐

Etnisitet/landbakgrunn: ☐ Norsk ☐ Ikke-norsk -spesifiser_____

Hvor mange brudd har du hatt etter fylte 50 år? (sett kun ett kryss) ☐ 1 ☐ 2 ☐ 3 eller flere

Etter at du fylte 50 år, har du hatt			Hvis JA, alder første gang	Fikk du bruddet i en trafikkulykke?	
Hoftebrudd/Lårhalsbrudd	☐ ja	☐ nei	☐☐	☐ ja	☐ nei
Håndleddsbrudd?	☐ ja	☐ nei	☐☐	☐ ja	☐ nei
Brudd i skulder?	☐ ja	☐ nei	☐☐	☐ ja	☐ nei
Annet brudd?	☐ ja	☐ nei	☐☐	☐ ja	☐ nei

Har din mor eller far hatt hoftebrudd/lårhalsbrudd? ☐ Ja ☐ Nei

Har du eller har du hatt noen av disse tilstandene/sykdommene?			Alder første gang	Antall år syk
Beinskjørhet	☐ ja	☐ nei	☐☐	☐☐
Diabetes/sukkersyke	☐ ja	☐ nei	☐☐	☐☐
Hjerneslag/hjerneblødning	☐ ja	☐ nei	☐☐	☐☐
Lavt stoffskifte	☐ ja	☐ nei	☐☐	☐☐
Høyt stoffskifte	☐ ja	☐ nei	☐☐	☐☐
Kreftsykdom	☐ ja	☐ nei	☐☐	☐☐
Hjerteinfarkt	☐ ja	☐ nei	☐☐	☐☐
Angina	☐ ja	☐ nei	☐☐	☐☐
Hjerteflimmer	☐ ja	☐ nei	☐☐	☐☐
Leddgikt (Revmatoid artritt)	☐ ja	☐ nei	☐☐	☐☐
Nyresykdom	☐ ja	☐ nei	☐☐	☐☐
Astma/Kronisk obstruktiv lungesykdom (KOLS)	☐ ja	☐ nei	☐☐	☐☐
Kronisk tarmsykdom (f.eks.Cøliaki,Ulcerøs kolitt,Morbus Crohn)	☐ ja	☐ nei	☐☐	☐☐
Magesår/magekatarr	☐ ja	☐ nei	☐☐	☐☐
Er du blitt slankeoperert eller har du fått fjernet en del av magesekk/tarm	☐ ja	☐ nei	☐☐	☐☐
Har du redusert syn (f.eks.grå stær)	☐ ja	☐ nei	☐☐	☐☐
Annen kronisk sykdom, hvilken _____ _____	☐ ja	☐ nei	☐☐	☐☐

Draft

Løpenr.: ☐☐☐☐ ☐☐☐☐☐

Fyll inn for hver linje om du bruker noen av følgende medisiner eller tar tilskudd			**Antall år brukt**
Medisin mot beinskjørhet (f.eks.Alendronat,Fosamax,Aclasta,Prolia,Forsteo)	☐ ja	☐ nei	☐☐
Kortisontabletter (f.eks.Prednisolon,Medrol)	☐ ja	☐ nei	☐☐
Vanndrivende eller annen medisin mot høyt blodtrykk	☐ ja	☐ nei	☐☐
Kolesterolsenkende medisin	☐ ja	☐ nei	☐☐
Sovemedisiner, sterke smertestillende medisiner eller beroligende medisin	☐ ja	☐ nei	☐☐
Insulin	☐ ja	☐ nei	☐☐
Tabletter mot sukkersyke	☐ ja	☐ nei	☐☐
Syrenøytraliserende tabletter for sure oppstøt og plager fra mage/spiserør	☐ ja	☐ nei	☐☐
Kalktabletter	☐ ja	☐ nei	☐☐
Vitamin D tilskudd (tran,trankapsler,vitamin D dråper/tabletter,multivitamin)	☐ ja	☐ nei	☐☐
Andre medisiner _____	☐ ja	☐ nei	☐☐
_____			

Har du falt i løpet av de siste 12 måneder?	**Har du fått lavere kroppshøyde?**	**Bruker du ganghjelpemiddel?**
☐ nei	☐ Nei	☐ nei
☐ ja, 1 gang	☐ ja, (1-5 cm)	☐ ja, (stokk/krykke)
☐ ja, 2 ganger	☐ ja, (5-10 cm)	☐ ja, (rullator/prekestol)
☐ ja, 3 eller flere	☐ ja, (over 10 cm)	☐ ja, (rullestol)

Hvor ofte driver du mosjon? f.eks. går en tur, går på ski, svømmer eller driver trening/idrett (sett kun ett kryss)

☐ Aldri ☐ 1 gang i uka ☐ 2-3 ganger i uka ☐ 4-7 ganger i uka

Hvor lenge mosjonerer du i gjennomsnitt hver gang? (sett kun ett kryss)

☐ Mindre enn 15 minutter ☐ 15-29 minutter ☐ 30 minutter- 1 time ☐ over 1 time

Drikker du melk, kaffe latte, spiser yoghurt eller osteskiver daglig?

☐ Nei ☐ ja, 1-2 enheter ☐ ja, 3-4 enheter ☐ ja, 5 eller flere enheter

Drikker du alkohol daglig? (en øl, ett glass vin eller en drink)

☐ Nei ☐ ja, 1-2 ☐ ja, 3 eller flere

Røyker du daglig? (gjelder også e-sigaretter og røykeplaster) ☐ Nei ☐ ja

Snuser du daglig? ☐ Nei ☐ ja

Løpenr.: ☐☐☐☐ ☐☐☐☐☐

Er du i jobb? (sett kun ett kryss)

- ☐ Ja, 100%
- ☐ Ja, deltid angi % ☐☐
- ☐ Nei
- ☐ Pensjonist

Hvordan er din bosituasjon? (sett kun ett kryss)

- ☐ Hjemme uten hjelp
- ☐ Hjemmesykepleie/hjemmehjelp, antall timer/uke ☐☐
- ☐ Hjemme med hjelp av familie/venner, antall timer/uke ☐☐
- ☐ Sykehjem

Hvordan vurderer du din egen helse sånn i alminnelighet? (sett kun ett kryss)

☐ Meget god ☐ God ☐ Verken god eller dårlig ☐ Dårlig ☐ Meget dårlig

EQ-5D Under hver overskrift ber vi deg krysse av den ene boksen som best beskriver din helse I DAG

5 Gange, *velg kun en av følgende:*

- ☐ Jeg har ingen problemer med å gå omkring
- ☐ Jeg har litt problemer med å gå omkring
- ☐ Jeg har middels store problemer med å gå omkring
- ☐ Jeg har store problemer med å gå omkring
- ☐ Jeg er ute av stand til å gå omkring

6 Personlig stell, *velg kun en av følgende:*

- ☐ Jeg har ingen problemer med å vaske eller kle meg
- ☐ Jeg har litt problemer med å vaske eller kle meg
- ☐ Jeg har middels problemer med å vaske eller kle meg
- ☐ Jeg har store problemer med å vaske eller kle meg
- ☐ Jeg er ute av stand til å vaske eller kle meg

7 Vanlige gjøremål, *velg kun en av følgende:*

- ☐ Jeg har ingen problemer med å utføre mine vanlige gjøremål
- ☐ Jeg har litt problemer med å utføre mine gjøremål
- ☐ Jeg har middels store problemer med å utføre mine gjøremål
- ☐ Jeg har store problemer med å utføre mine gjøremål
- ☐ Jeg er ute av stand til å utføre mine vanlige gjøremål

8 Smerter/ubehag, *velg kun en av følgende:*

- ☐ Jeg har verken smerter eller ubehag
- ☐ Jeg har litt smerter eller ubehag
- ☐ Jeg har middels sterke smerter eller ubehag
- ☐ Jeg har sterke smerter eller ubehag
- ☐ Jeg har svært sterke smerte eller ubehag

9 Angst/depresjon, *velg kun en av følgende:*

- ☐ Jeg er verken engstelig eller deprimert
- ☐ Jeg er litt engstelig eller deprimert
- ☐ Jeg er middels engstelig eller deprimert
- ☐ Jeg er svært engstelig eller deprimert
- ☐ Jeg er ekstremt engstelig eller deprimert

Løpenr.: ☐☐☐☐ ☐☐☐☐☐

Bare for menn med kreft i prostata

Får du hormonbehandling mot kreft i prostata? ☐ Nei ☐ ja

Bruker du nå Alendronat, Optinat, Zometa eller Prolia som ledd i behandlingen mot prostatakreft? ☐ Nei ☐ ja

Bare for kvinner

Tar du hormoner mot plager i overgangsalder? (tabletter eller plaster, vi mener ikke Ovesterin)

☐ Nei ☐ ja

Bruker du Femar, Arimidex, Anastrozole, Letrazole, Letrozol eller Aromasin mot brystkreft?

☐ Nei ☐ ja

Har menstruasjonen stoppet?

☐ Nei ☐ ja Hvis ja, hvor gammel var du da menstruasjonen stoppet ☐☐

Hvis menstruasjonen har stoppet, hvorfor har menstruasjonen stoppet? (sett kun ett kryss)

☐ Den stoppet av seg selv
☐ Operert bort begge eggstokkene
☐ Fjernet livmor
☐ Strålebehandling/cellegift

Hvis du har barn, hvor mange barn har du født? Antall ☐☐

Hvor mange måneder ammet du dem tilsammen? Antall mnd. ☐☐

Kommentarer_____

_____

_____

Takk for hjelpen

Paper I

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Full Length Article

High prevalence of vertebral fractures and low trabecular bone score in patients with fragility fractures: A cross-sectional sub-study of NoFRACT

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ABSTRACT

Purpose: Norway has among the highest incidence rates of fractures in the world. Vertebral fracture assessment (VFA) and trabecular bone score (TBS) provide information about fracture risk, but their importance have not been studied in Norwegian patients with fragility fractures. The objectives of this study were to examine the clinical characteristics of a cohort of women and men with fragility fractures, their prevalence of vertebral fractures using VFA and prevalence of low TBS, and explore the differences between the sexes and patients with and without vertebral fractures.

Methods: This cross-sectional sub-study of the Norwegian Capture the Fracture Initiative (NoFRACT) included 839 patients with fragility fractures. Of these, 804 patients had bone mineral density (BMD) of the total hip, femoral neck and/or spine assessed using dual energy x-ray absorptiometry, 679 underwent concomitant VFA, 771 had TBS calculated and 696 responded to a questionnaire.

Results: Mean age was 65.8 (SD 8.8) years and 80.5% were women. VFA revealed vertebral fractures in 34.8% of the patients and 34.0% had low TBS ($\leq$ 1.23), with no differences between the sexes. In all patients with valid measures of both VFA and TBS, 53.8% had either vertebral fractures, low TBS, or both. In the patients with osteopenia at the femoral neck, 53.6% had either vertebral fractures, low TBS, or both. Femoral neck BMD T-score ≤ -2.5 was found in 13.8% of all patients, whereas the corresponding figure was 27.4% using the skeletal site with lowest T-score. Women exhibited lower BMD at all sites and lower TBS than men (1.27 vs. 1.29), (all $p < 0.05$). Patients with prevalent vertebral fractures were older (69.4 vs. 64.0 years), exhibited lower BMD at all sites and lower TBS (1.25 vs.1.29) than those without vertebral fractures (all $p < 0.05$). Before assessment, 8.2% were taking anti-osteoporotic drugs (AOD), and after assessment, the prescription rate increased to 56.2%.

Conclusions: More than half of the patients with fragility fractures had vertebral fractures, low TBS or both. The

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prescription of AOD increased seven fold from before assessment to after assessment, emphasizing the importance of risk assessment after a fragility fracture.

1. Introduction

Norway has among the highest rates of hip and forearm fractures in the world [1,2] and the highest prevalence of vertebral fractures in Europe [3]. Mortality is high, especially following hip and vertebral fractures [4,5], as is morbidity, with considerable impact on quality of life and high health economic costs [6]. Still, secondary fracture prevention in Norway is suboptimal. After a hip fracture, only 15% of women and 4% of men received treatment with anti-osteoporotic drugs (AOD) [7]. To meet this challenge, the Norwegian Capture the Fracture Initiative (NoFRACT) was established to improve secondary fracture prevention by introducing a Fracture Liaison Service (FLS) model of care at seven hospitals in Norway [8].

In risk assessment following a fragility fracture, a broad diagnostic approach is required, because more than half of the patients reveal bone mineral density (BMD) T-scores in the osteopenic range [9,10]. Information on clinical risk factors is important and additional information on bone strength is desirable to make correct treatment decisions. Vertebral fracture assessment (VFA) and Trabecular bone score (TBS) calculations are easily accessible approaches when using dual energy x-ray absorptiometry (DXA). VFA provides information on number and grade of compression of fractured vertebrae, which is related to future fracture risk [11]. TBS is a textural index of trabecular bone structure obtained from anterior-posterior DXA images of the lumbar spine that predicts fractures independently of BMD in women [12–14] and men [15]. TBS has been reported to add value beyond BMD for identification of vertebral fractures in the non-osteoporotic range [16,17]. Studies on VFA and TBS in Norwegian patients with fragility fractures are, however, lacking.

The aims of this study were to i) examine the clinical characteristics of a cohort of Norwegian women and men with fragility fractures, along with their prevalence of vertebral fractures using VFA and prevalence of low TBS, and ii) explore the differences in BMD T-score and TBS between sexes and between patients with and without prevalent vertebral fractures.

2. Materials and methods

2.1. Study subjects

NoFRACT is an ongoing multicenter study in the orthopedic departments at 7 hospitals in Norway and 23,578 patients were enrolled by Jan 2018 [8]. The objectives are to improve secondary fracture prevention by introducing a standardized intervention program consisting of an FLS model of care for identification, assessment and treatment of osteoporosis in patients with fragility fractures. NoFRACT will investigate the effect of this intervention on the rate of subsequent fractures. All women and men 50 years and older with a recently diagnosed fragility fracture are eligible to the intervention. Those with fractures of fingers, toes, skull and face are ineligible. The coordinating nurse identifies patients based on ICD-10 codes and eligibility criteria, and provides information on the project either in person or in a letter to in- and outpatients, and information on lifestyle advice, sufficient intake of calcium and vitamin D through diet or supplementation and fall prevention. Blood samples are obtained to rule out common causes for secondary osteoporosis. Patients are individually evaluated and treated according to comorbidities and preferences. AOD (mainly alendronate or zoledronic acid) are offered to patients with hip fracture, vertebral fracture or 2 or more fragility fractures regardless of BMD T-score or 10-year probability of major osteoporotic fracture calculated using the Fracture Risk Assessment Tool (FRAX). Patients with their first fragility fracture are offered DXA for assessment of BMD T-score of both hips and spine, and/or FRAX score calculation. Treatment is offered to those with a BMD T-score ≤ -1.5 or FRAX score $\geq 20\%$.

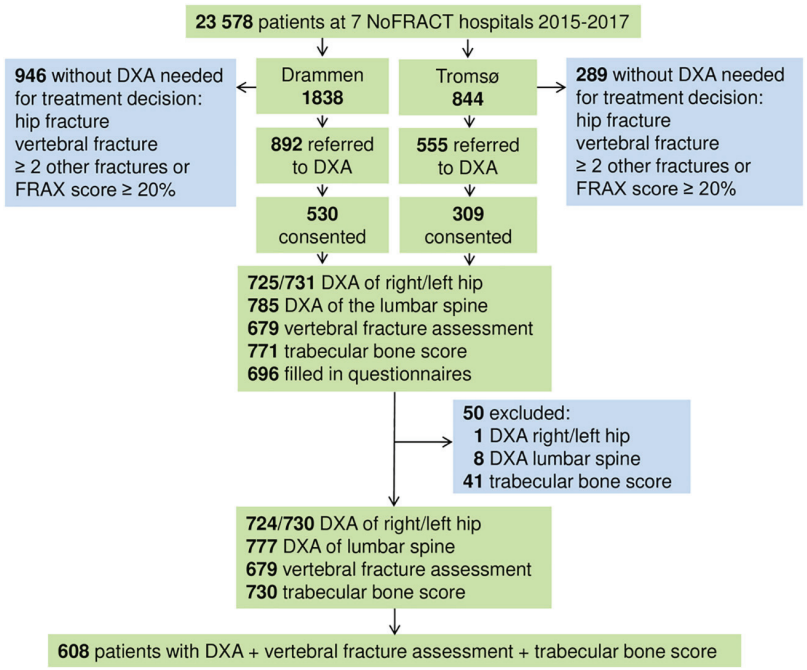

Fig. 1. Patients in the Norwegian Capture the Fracture Initiative (NoFRACT) sub-study.
DXA, dual energy x-ray absorptiometry; FRAX, 10-year probability of major osteoporotic fracture calculated using the Fracture Risk Assessment Tool (FRAX).

This consent based sub-study (NoFRACTsub: NCT02608801) of NoFRACT (NoFRACT: NCT02536898) is ongoing at 2 of the 7 hospitals (Fig. 1). Patients were recruited among those who were referred to DXA at the University Hospital of North Norway (UNN), Tromsø from 1 Oct 2015 to 31 Dec 2017 (n = 844) and the Drammen Hospital in south/eastern part of Norway from 1 Jan 2016 to 31 Dec 2017 (n = 1838). At these 2 hospitals, over 90% of the patients with fragility fractures were identified and offered assessment. Patients with communication problems, cognitive dysfunction, or short life expectancy, were not eligible to the sub-study. Some patients were not included due to lack of time or interest, or difficulties with follow-up. Although DXA was not needed for treatment decision for those with hip fracture, vertebral fracture or multiple fractures, we performed DXA in as many as possible, because baseline values are useful during follow-up.

Of 839 patients (309 in Tromsø and 530 in Drammen), 696 completed a questionnaire. Of 725/731 patients who had a DXA scan of the right/left hip, one patient was excluded due to poor imaging quality. Of 785 patients who had an anteroposterior DXA scan of the lumbar spine, 8 patients were excluded due to anatomical aberrations, degenerative or postoperative changes in three or more vertebrae. VFA was performed in 679 patients. Of 771 patients with TBS calculated, 26 were excluded due to body mass index (BMI) > 37 kg/m^2 and 15 were excluded due to three or more abnormal lumbar vertebrae. Hence, 724/730 patients with DXA scans of the right/left hip, 777 with DXA of the lumbar spine, 679 with VFA and 730 with TBS calculated were included in the analyses. The proportion of vertebrae that could not be assessed due to low imaging quality was 8.4%, mainly in the upper thoracic region (T4–6). A total of 608 patients had both DXA and VFA performed and also TBS calculated. All patients in this sub-study provided written informed consent. The study was approved by The Regional Committee for Medical and Health Research Ethics (REK 2014/2260) and was conducted in accordance with the World Medical Association Declaration of Helsinki.

Table 1
Characteristics of all 839 patients with fragility fracture and stratified by sex.

	n	All	Women	Men
n (%)	839	839	675 (80.5)	164 (19.5)[c]
Age (years)	839	65.8 ± 8.8	65.6 ± 8.7	66.7 ± 9.2
Caucasian, n (%)	839	815 (97.0)	655 (96.9)	160 (97.6)
Height (cm)	784	167.1 ± 8.2	164.6 ± 6.2	177.7 ± 6.9[c]
Weight (kg)	784	75.0 ± 14.8	72.2 ± 13.3	86.9 ± 15.4[c]
Body mass index (kg/m$^{2)}$	784	26.8 ± 4.6	26.7 ± 4.6	27.4 ± 4.1
Index fracture	839			
Hip, n (%)		73 (8.7)	49 (7.3)	24 (14.6)[b]
Forearm, n (%)		309 (36.8)	274 (40.6)	35 (21.3)[b]
Proximal humerus, n (%)		105 (12.5)	90 (13.3)	15 (9.2)
Vertebral, n (%)		50 (6.0)	40 (5.9)	10 (6.1)
Ankle, n (%)		148 (17.6)	110 (16.3)	38 (23.2)
Other sites, n (%)		154 (18.4)	112 (16.6)	42 (25.6)[a]
Fractures after age of 50 years	639			
1, n (%)		381 (59.6)	302 (57.6)	79 (68.7)[a]
2, n (%)		160 (25.0)	134 (25.5)	26 (22.6)
≥3, n (%)		98 (15.4)	88 (16.9)	10 (8.7)[a]
Fractures before index fracture, n (%)		258 (40.4)	222 (42.4)	36 (31.3)[a]
Prevalent vertebral fracture[d], n (%)	679	236 (34.8)	190 (34.6)	46 (35.7)
Trabecular Bone Score L1-L4	730	1.27 ± 0.11	1.27 ± 0.10	1.29 ± 0.12[a]
≥1.31, n (%)		274 (37.5)	215 (36.4)	59 (42.1)
1.23–1.31, n (%)		208 (28.5)	169 (28.7)	39 (27.9)
≤1.23, n (%)		248 (34.0)	206 (34.9)	42 (30.0)
Femoral neck BMD (g/cm^2)	730	0.816 ± 0.121	0.805 ± 0.116	0.866 ± 0.130[c]
Femoral neck T-score		−1.6 ± 0.9	−1.7 ± 0.8	−1.2 ± 0.9[c]
Normal, n (%)		155 (21.2)	103 (17.3)	52 (38.5)[c]
Osteopenia, n (%)		475 (65.0)	404 (67.8)	71 (52.6)[b]
Osteoporosis, n (%)		101 (13.8)	89 (14.9)	12 (8.9)
Total hip, BMD (g/cm^2)	730	0.865 ± 0.134	0.849 ± 0.126	0.938 ± 0.144[c]
Total hip T-score		−1.1 ± 1.1	−1.3 ± 1.0	−0.5 ± 1.1[c]
Lumbar spine BMD (g/cm^2)	777	1.058 ± 0.184	1.038 ± 0.178	1.145 ± 0.179[c]
Lumbar spine T-score		−1.1 ± 1.5	−1.3 ± 1.4	−0.4 ± 1.4[c]
Lowest T-score of all sites	799	−1.9 ± 1.0	−2.0 ± 1.0	−1.5 ± 1.0[c]
Normal, n (%)		120 (15.0)	76 (11.8)	44 (28.8)[c]
Osteopenia, n (%)		460 (57.6)	372 (57.6)	88 (57.5)
Osteoporosis, n (%)		219 (27.4)	198 (30.6)	21 (13.7)[b]
Supplementation before assessment				
Vitamin D, n (%)	690	457 (66.2)	378 (67.5)	79 (60.8)
Calcium, n (%)	687	146 (21.3)	129 (23.1)	17 (13.3)[a]
Prescription of AOD				
Before assessment, n (%)	729	60 (8.2)	57 (9.6)	3 (2.2)[b]
New after assessment, n (%)	737	354 (48.0)	315(52.6)	39 (28.3)[c]
Total after assessment, n (%)	737	414 (56.2)	372 (62.2)	42 (30.5)[c]

Values are mean ± SD or n (%). The variation in total numbers was due to some missing data.
BMD, bone mineral density; AOD, anti-osteoporotic drugs.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$ compared to women.
[d] Prevalent vertebral fracture, included semiquantitative (SQ) score of SQ1, SQ2 and SQ3 fractures.

2.2. Variables

The index fractures that led to inclusion were hip fractures (femoral neck, trochanteric and subtrochanteric), forearm fractures, proximal humerus fractures, vertebral fractures (thoracic- or lumbar spine), ankle fractures (one, two or both malleoli), and other fractures. Vertebral fractures that led to inclusion in the study were identified on x-ray, CT or MRI, not using VFA. The prevalent vertebral fractures included only vertebral fractures revealed using VFA.

Information on number and type of fractures after the age of 50, supplementation of calcium and vitamin D and current use of AOD was collected through a questionnaire. Information on new prescriptions of AOD after assessment was obtained from medical records.

Height and weight were measured, and BMI was calculated as weight (kg) per square meter height. BMD was measured at femoral neck and total hip at both sides and lumbar spine (L1-L4) using DXA (GE Lunar, Prodigy Pro, Madison, WI, USA) in Tromsø and iDXA (GE Lunar, Pro, Madison, WI, USA) in Drammen. Daily phantom Quality Assurance (QA) of the DXA equipment was performed. Fractured lumbar vertebrae were excluded. Left hip was used in the calculations of BMD T-score of femoral neck and total hip. Osteoporosis was defined as femoral neck BMD T-score ≤ -2.5, and osteopenia as a femoral neck BMD T-score between ≤ -1.0 and -2.5 according to the World Health Organization (WHO) DXA-criteria [18], using the Third National Health and Nutrition Examination Survey reference data [19]. The proportion of patients with osteoporosis and osteopenia at the site with the lowest T-score (femoral neck, total hip or lumbar spine), was calculated as recommended by the International Society of Clinical Densitometry (ISCD) [20]. Female reference population was used for men.

Lateral thoracolumbar spine (T4-L4) images were obtained with the patient in a lateral decubitus position with lumbar support and hips flexed 90 degrees. VFA of the fracture severity was performed by an experienced physician (TTB) using the semiquantitative (SQ) vertebral deformity scoring method by Genant [21]. This combines the visual examination of deformation of the vertebral body (height loss of the anterior, middle, posterior or the whole vertebra) and grading of the vertebrae after proportion of height loss. A SQ score of 0 (SQ0) (< 20% height loss) was considered as a normal, non-fractured vertebra, SQ1 (20–25% height loss) as a mild fracture, SQ2 (25–40% height loss) as a moderate fracture, and SQ3 ($\geq$ 40% height loss) as a severe fracture. In addition, the exact SQ grading of height loss of the fractured vertebrae was performed morphometrically within Encore with manually six-point labelling [21]. Deformities identified as Schmorl's or Modic lesions, short vertebral height, extensive degenerative changes with deformation and physiological wedging of vertebrae were not counted as fractures. An experienced ISCD certificated clinical technician (MBS), who was blinded to the initial results, reviewed a random sample of 200 lateral spine images. Spinal deformity index (SDI) was calculated as the sum of the SQ score of all T4-L4 vertebrae; SQ0 = 0 points, SQ1 = 1 point, SQ2 = 2 points and SQ3 = 3 points [22].

TBS was calculated from the DXA scans used for lumbar spine BMD (L1-L4) using TBS iNsight software (Madimaps, Geneva, Switzerland) version 3.0.1. Fractured vertebrae were excluded. The reference population was the European (Medimaps) for both sexes. The TBS values were divided into three groups, as recommended by Medimaps (TBS insight user guide TM-001-02), and based on a meta-analysis of fracture risk assessment as a function of TBS utilizing 14 prospective population-based cohorts of 17,809 women and men. The estimated fracture risk was: high TBS $\geq$ 1.31 (low fracture risk), TBS between 1.23 and 1.31 (intermediate fracture risk), and low TBS $\leq$ 1.23 (high fracture risk)

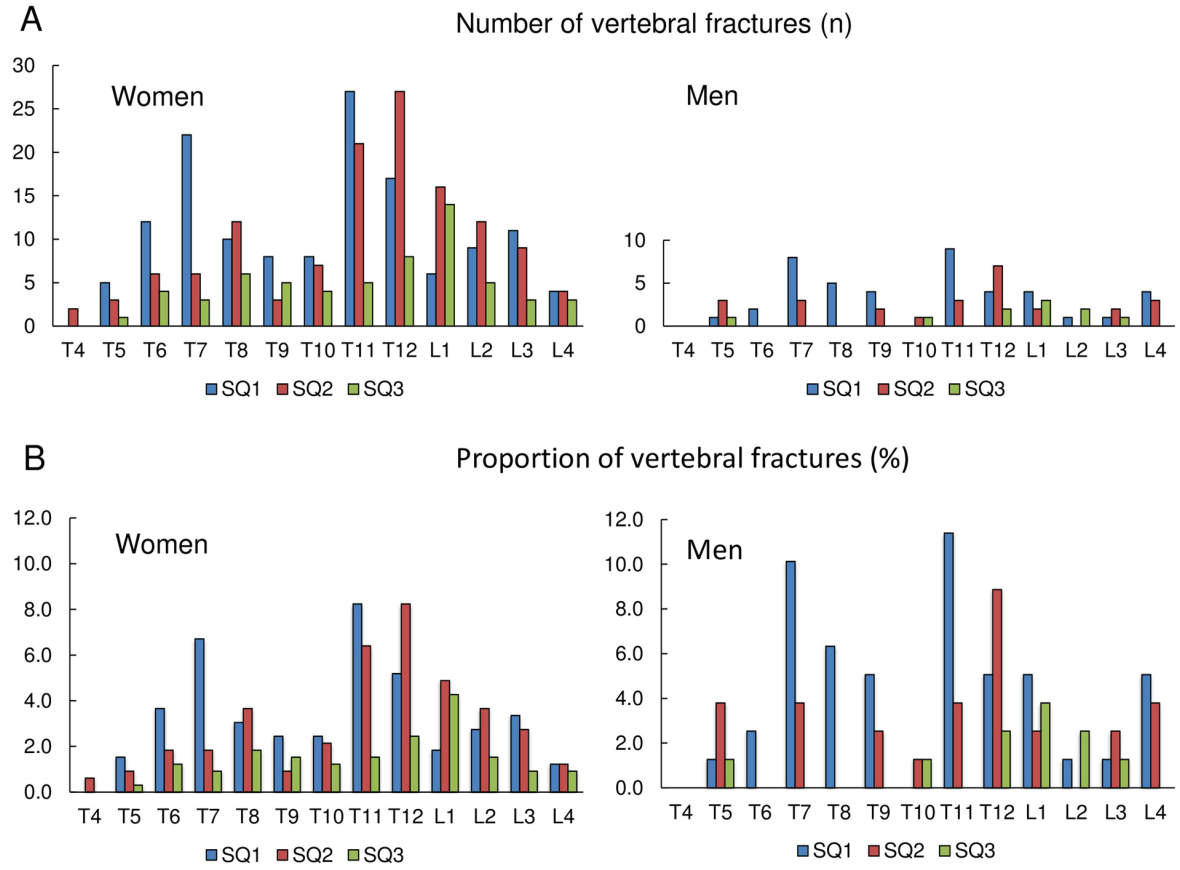

Fig. 2. (A) The number and (B) the proportion, site and grade of compression of fractured vertebrae in women and men. Semi-quantitative (SQ) score 1 = mild fracture, SQ2 = moderate fracture, SQ3 = severe fracture, for each vertebra from thoracic and lumbar spine (T4 to L4).

[23].

2.3. Statistical analyses

Statistical analyses were performed using Stata (Version 15, StataCorp LP, TX, USA). Continuous variables were checked for normality with quantile-quantile (QQ) plots and reported as means with standard deviation (SD). Differences in means between groups were calculated using Student's *t*-test. Categorical variables were reported as number and percentage. Groups were compared using chi square test in samples > 100 and Fisher's exact test in smaller samples. The inter-observer agreement of the assessment of a vertebral fracture (SQ1-SQ3) was calculated using Cohen's Kappa value (κ) with quadratic weighting. The inter-observer agreement by grade of severity of the fractures, within each SQ group, was calculated using Cohen's κ without weighting. Landis and Koch guidelines were followed to interpret the levels of agreement by Cohen's κ: almost perfect agreement (κ > 0.81), substantial agreement (κ = 0.61–0.80), moderate agreement (0.41–0.60), fair agreement (0.21–0.40), slight agreement (0–0.20) and poor agreement (< 0) [24].

3. Results

3.1. Characteristics of all patients with fractures

In all the 839 patients, the distribution of the index fractures was 8.7% hip, 36.8% forearm, 12.5% proximal humerus, 6.0% vertebral, 17.6% ankle and 18.4% other types (Table 1). A total of 40.4% reported one or more fractures prior to the index fractures. In those with VFA, 34.8% had prevalent vertebral fractures. Mean TBS was 1.27, and 34.0% had low TBS. Osteoporosis was present at the femoral neck in 13.8% of the patients and in 27.4% at the site with lowest BMD T-score. Osteopenia was present at the femoral neck in 65.0% of the patients and in 57.6% at the site with lowest BMD T-score. Only 8.2% used AOD before assessment, 48.0% had a new prescription after assessment, thus a total of 56.2% had AOD prescribed after assessment.

3.2. Comparison of women and men

A total of 80.5% were women. Mean age did not differ between the sexes. Women exhibited a smaller proportion of hip fractures than men (7.3% vs. 14.6%, p = 0.005), but a larger proportion of forearm fractures (40.6% vs. 21.3%, p = 0.001). A larger proportion of women than men had sustained fractures before participating in the study (42.4% vs. 31.3%, p = 0.036). A higher number of women than men had vertebral fractures (190 vs. 46), but there was no difference in prevalence of vertebral fractures between sexes (34.6% vs. 35.7%, p = 0.837) (Table 1). Vertebral fractures were most prevalent at T7, T11 and T12 (Fig. 2). Mean TBS of L1-L4 was lower in women than men (1.27 vs. 1.29, p = 0.044), but the proportion with low TBS did not differ between the sexes. Mean BMD T-score of femoral neck, total hip, lumbar spine and lowest T-score of any site was lower in women than in men (all p < 0.001). A higher proportion of women than men had osteoporosis at the site with lowest T-score (30.6% vs. 13.7%, p = 0.008). More women than men had AOD prescribed before assessment (9.6% vs. 2.2%) and after assessment (62.2% vs. 30.5%), (both p < 0.01).

3.3. Comparison of patients with and without prevalent vertebral fractures

Patients with vertebral fractures were older (69.4 vs. 64.0 years), shorter (166.2 vs. 167.7 cm) and a larger proportion reported previous fractures compared to those without vertebral fractures (all p < 0.05, Table 2). Patients with vertebral fractures had lower mean TBS (1.25 vs. 1.29) and a larger proportion had low TBS (42.9% vs. 29.1%, both p < 0.001) than those without vertebral fractures. BMD at all sites were lower, and a higher proportion had osteoporosis at the femoral neck (16.9% vs. 9.5%) and at the site with lowest T-score (37.0% vs. 22.7%, all p < 0.05) in those with than without vertebral fractures. A larger proportion of patients with vertebral fractures on VFA had AOD prescribed after assessment (70.0% vs. 47.8%, p < 0.001).

3.4. Prevalence of vertebral fractures and low TBS

Of all 608 patients with BMD, VFA and TBS assessed, 53.8% had either vertebral fracture, low TBS, or both (Fig. 3A). Only 13.2% of

Table 2
Comparison of characteristics in patients with and without vertebral fractures on vertebral fracture assessment.

	n	With vertebral fracture[d] (n = 236)	Without vertebral fracture (n = 443)
Women, n (%)	679	190 (80.5)	360 (81.3)
Age (years)	679	69.4 ± 7.9	64.0 ± 8.4[c]
Height (cm)	663	166.2 ± 8.0	167.7 ± 8.0[a]
Weight (kg)	663	73.5 ± 14.3	75.3 ± 15.0
Body mass index (kg/m^2)	663	26.5 ± 4.2	26.7 ± 4.6
Index fracture	679		
Hip, n (%)		21 (8.9)	29 (6.6)
Forearm, n (%)		73 (30.9)	197 (44.5)[b]
Proximal humerus, n (%)		31 (13.1)	48 (10.8)
Vertebral, n (%)		34 (14.4)	5 (1.1)[c]
Ankle, n (%)		33 (14.0)	90 (20.3)[a]
Other sites, n (%)		44 (18.7)	74 (16.7)
Fractures after age of 50 years	526		
1, n (%)	308	80 (43.5)	228 (66.7)[c]
2, n (%)	137	60 (32.6)	77 (22.5)[a]
≥3, n (%)	81	44 (23.9)	37 (10.8)[c]
Trabecular Bone Score L1-L4 (SD)	625	1.25 ± 0.10	1.29 ± 0.10[c]
≥1.31, n (%)		63 (29.7)	172 (41.6)[b]
1.23–1.31, n (%)		58 (27.4)	121 (29.3)
≤1.23, n (%)		91 (42.9)	120 (29.1)[b]
Femoral neck BMD (g/cm^2)	635	0.786 ± 0.115	0.830 ± 0.116[c]
Femoral neck T-score		−1.8 ± 0.8	−1.5 ± 0.8[c]
Normal, n (%)		65 (27.5)	126 (28.4)
Osteopenia, n (%)		131 (55.5)	275 (62.1)
Osteoporosis, n (%)		40 (16.9)	42 (9.5)[b]
Total hip BMD (g/cm^2)		0.831 ± 0.135	0.881 ± 0.129[c]
Total hip T-score		−1.4 ± 1.1	−1.0 ± 1.0[c]
Lumbar spine BMD (g/cm^2)	656	1.023 ± 0.181	1.076 ± 0.179[c]
Lumbar spine T-score		−1.4 ± 1.4	−1.0 ± 1.4[c]
Lowest T-score of all sites	670	−2.1 ± 1.0	−1.8 ± 1.0[c]
Normal, n (%)		23 (10.0)	72 (16.4)[a]
Osteopenia, n (%)		122 (53.0)	268 (60.9)
Osteoporosis, n (%)		85 (37.0)	100 (22.7)[c]
Supplementation before assessment			
Vitamin D, n (%)	559	137 (70.6)	238 (65.2)
Calcium, n (%)	558	54 (28.0)	67 (18.4)[b]
Prescription of AOD			
Before assessment, n (%)	602	19 (9.3)	24 (6.0)
New after assessment, n (%)	606	125 (60.7)	167 (41.8)[c]
Total after assessment, n (%)		144 (70.0)	191 (47.8)[c]

Values are mean ± SD or n (%). The variation in total numbers was due to some missing data.
BMD, bone mineral density; AOD, anti-osteoporotic drugs.
[a] p < 0.05.
[b] p < 0.01.
[c] p < 0.001 compared to those with vertebral fracture.
[d] Vertebral fracture, included semiquantitative (SQ) score of SQ1, SQ2 and SQ3 fractures.

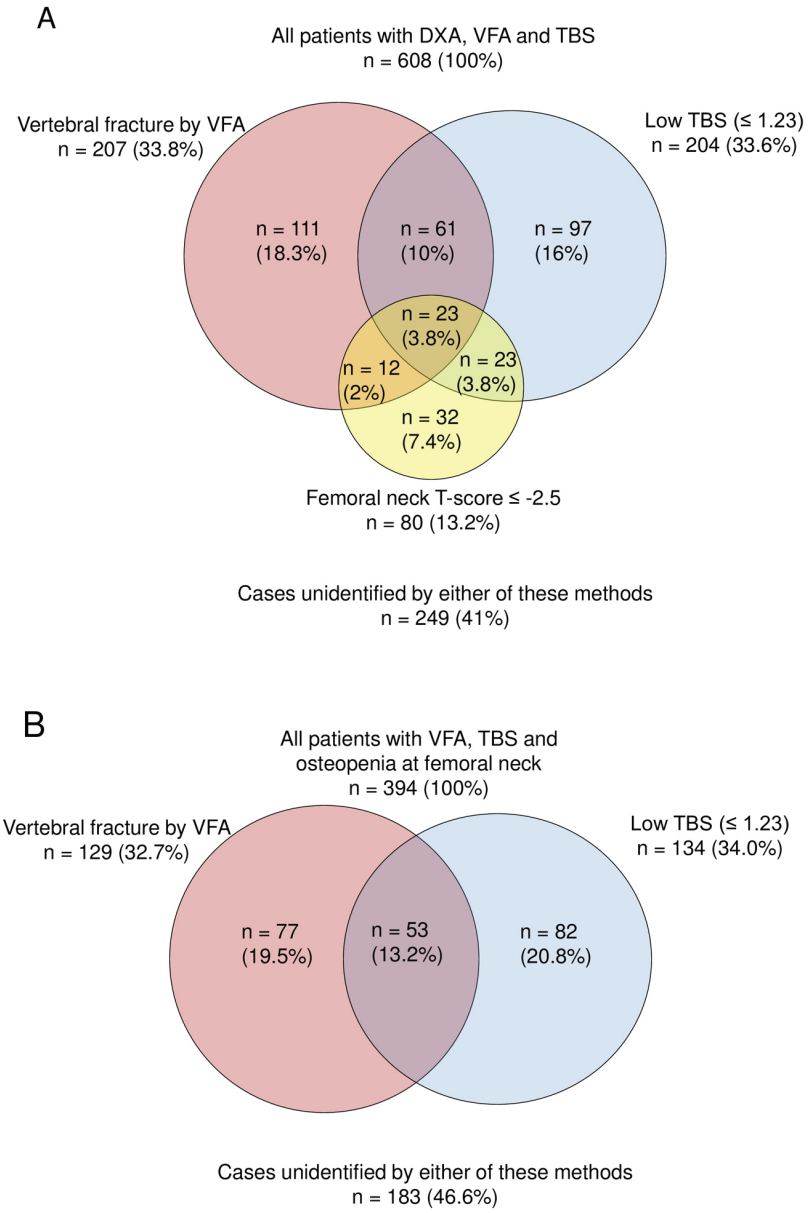

Fig. 3. Proportion of (A) all fracture patients with dual energy x-ray absorptiometry (DXA), vertebral fracture assessment (VFA) and trabecular bone score (TBS) (n = 608) who had vertebral fractures, low TBS, or both, and osteoporosis of the femoral neck, and B) fracture patients with osteopenia of the femoral neck (n = 394) with vertebral fracture, low TBS, or both.

them had osteoporosis at the femoral neck. Of 394 with osteopenia at the femoral neck, 53.6% had either vertebral fracture, low TBS or both (Fig. 3B).

Of a total of 8827 imaged vertebrae, 8.4% were excluded because of insufficient image quality (Table 3). Of the evaluable vertebrae 5% had a fracture, 44.7, 37.8 and 17.5% were SQ1, SQ2 and SQ3 fracture, respectively. A total of 34.8% of the patients had a SQ1, SQ2 or SQ3 fracture, while after exclusion of SQ1 fractures, 20.3% had a SQ2 or SQ3 fracture. The prevalence of vertebral fracture or SDI did not differ between sexes. The inter-observer agreement of SQ1-SQ3 fractures was almost perfect with a κ of 0.84 (95% CI: 0.70, 0.98). Inter-observer agreement of SQ1 and SQ2 fractures was moderate with a κ of 0.48 (95% CI: 0.34, 0.61) and 0.55 (95% CI: 0.41, 0.69), respectively. Inter-observer agreement of SQ3 fractures could only be calculated at T8, T9 and L2 due to few observations with a κ of 0.66 (95% CI: 0.53, 0.80).

4. Discussion

In this cohort of Norwegian patients with fragility fractures, one in three had vertebral fractures on VFA, one in three had low TBS, and more than half of the patients had either vertebral fractures, low TBS or both. The majority of the patients had osteopenia. A small proportion had osteoporosis at the femoral neck, but this proportion was larger when using the site with lowest BMD T-score. Women had lower BMD and TBS than men. Patients with vertebral fractures were older and had lower BMD and TBS than those without vertebral fractures. The prescription of AOD increased 7 fold, and about half of the patients were prescribed AOD after the assessment, more women than men, and more patients with than without vertebral fractures.

We found higher prevalence of vertebral fractures of 35% compared to a FLS cohort in Scotland where 19–20% of women and men of 50 years and older with non-vertebral fractures had a vertebral fracture

Table 3
Vertebral fracture assessment of 8827 vertebrae in 679 patients.

	Total	Women	Men
Patients, n (%)	679	550 (81.0)	129 (19.0)
Imaged vertebrae, n (%)	8827	7150	1677
Excluded vertebrae, n (%)	742 (8.4)	600 (8.4)	142 (8.5)
Evaluable vertebrae, n (%)	8085 (91.6)	6550 (91.6)	1535 (91.5)
Vertebrae without fracture (SQ0), n (%)	7678 (95.0)	6222 (95.0)	1456 (94.9)
Vertebras with fracture	407 (5.0)	328 (5.0)	79 (5.1)
SQ1 deformity, n (%)	182 (44.7)	139 (42.4)	43 (54.4)
SQ2 deformity, n (%)	154 (37.8)	128 (39.0)	26 (32.9)
SQ3 deformity, n (%)	71 (17.5)	61 (18.6)	10 (12.7)
Patients with vertebral fracture			
SQ0, with no fractured vertebra, n (%)	443 (65.2)	360 (65.4)	83 (64.3)
SQ1 mild fractures, n (%)	145 (21.4)	114 (20.7)	31 (24.0)
SQ2 moderate fractures, n (%)	113 (16.6)	93 (16.9)	20 (15.5)
SQ3 severe fractures, n (%)	49 (7.2)	39 (7.1)	10 (7.8)
SQ1-SQ3 fractures, n (%)	236 (34.8)	190 (34.6)	46 (35.7)
SQ2-SQ3 fractures, n (%)	138 (20.3)	115 (20.1)	23 (17.8)
Spinal deformity index			
0, n (%)	443 (65.2)	360 (65.4)	83 (64.3)
1, n (%)	80 (11.8)	63 (11.5)	17 (13.2)
2, n (%)	63 (9.3)	53 (9.6)	10 (7.8)
3, n (%)	38 (5.6)	31 (5.6)	7 (5.4)
≥4, n (%)	55 (8.1)	43 (7.8)	12 (9.3)

SQ, semiquantitative score.
There was no significant difference between the sexes.

[25]. The prevalence of vertebral fracture was 37% in another FLS cohort of women and men in France, which was similar to our findings [16]. However, those patients were older than in our cohort (age of 74 vs. 66 years), and a higher proportion had hip fracture (51 vs. 9%) [16]. In population-based studies, the prevalence of vertebral fracture was 19–20% in women and men over 70 years in Norway [26] and 16–19% in the European Vertebral Osteoporosis Study, with the highest rates in the Scandinavian countries [3]. As a prior fracture, non-vertebral and vertebral, increases the risk for a subsequent fracture, fracture cohorts have higher prevalence of vertebral fracture than do the general population as shown in population-based studies, and they have more comorbidity [3,16,25,26]. Although a higher number of women than men had a vertebral fracture we found no difference between sexes in prevalence of vertebral fractures in percentage terms. Despite of the differences in prevalence of vertebral fracture between studies; the prevalence tended to be similar in both sexes within each study.

Identifying those with vertebral fractures is challenging because few of them come to the hospital for an x-ray or other examination [27]. The large proportion of vertebral fractures in this fracture cohort is interesting because vertebral fractures increase the risk of new fracture up to five fold [28,29]. Of all fractured vertebrae in our study, 45% were mild fractures (SQ1) compared to 5% in a general population [26]. One reason for the identification of so many SQ1 fractures may be that the images were obtained using new DXA machines with good image quality, particularly the iDXA. There have been some discussions regarding the SQ1 fractures, whether the majority are not true osteoporotic fractures. However, we carefully checked that physiological wedging and other deformities were not misclassified as a SQ1 fracture. Other methods may capture better the small fractures, even fractures with less height loss than 20%. After we excluded the SQ1 fractures, the prevalence of vertebral fractures (SQ2 and SQ3) was 20% in women and 18% in men, which is similar to the findings in the fracture cohort from Scotland [25].

Another interesting finding was the seven fold increased AOD prescription (from 8% before to 56% after the assessment). This is in agreement with other studies that have introduced FLS where an increase in AOD prescription from 5-19% before assessment to 51–73% after assessment is described [30,31], and that illuminates the treatment gap and importance of assessing patients after a fragility fracture. We used treatment criteria based upon fracture (hip, vertebral, 2 or more fragility fractures), reduction in BMD T-score ≤ -1.5 and/or high FRAX score $\geq 20\%$, which contributed to the high AOD prescription rate in this study. TBS was not included among the criteria we used for treatment initiation. ISCD does not support use of TBS alone for treatment decision making and recommends that the TBS-adjusted FRAX score should be used. A large proportion had low TBS and vertebral fracture in our fracture cohort as shown in Fig. 3. This may be due to the cross-sectional design of the study that included only patients with fractures and no fracture-free controls.

To our knowledge, this is the first Scandinavian study on patients with fragility fractures described with both VFA and TBS, in addition to clinical risk factors and BMD. However, our study has some limitations. Only patients in need of a DXA examination and who were healthy enough to undergo follow-up were invited to this sub-study. This resulted in a healthy selection bias with a relatively small proportion of hip fractures in this sub-study. Without this bias, we could have had a higher proportion of patients with osteoporosis, vertebral fractures and low TBS. Although we tried to avoid observation bias, the two centers differed at some points. The Prodigy Pro DXA scanner in Tromsø had lower resolution and quality of the lateral spine images, and thus more non-evaluable vertebrae, compared to images obtained using the iDXA Pro in Drammen. However, none of the lateral images had too low quality for VFA, so all images were evaluated. The same experienced physician performed all the VFA, and the inter-observer agreement of the assessment of vertebral fractures was almost perfect. This is in agreement with prior studies that have reported small inter-observer variation [21].

In conclusion, vertebral fractures, low TBS, or both were present in more than half of women and men who were assessed after a fragility fracture. The prescription of AOD increased seven fold from before to after assessment, emphasizing the importance of risk assessment after a fragility fracture.

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Authors' roles

TTB, ÅB and EFE have led the design of this sub-study. TTB, ÅB, LBS, and TB designed the questionnaires. TTB, ÅB, CA, and MBS led the patient involvement and data collection. All authors contributed to methodological decisions, data interpretation, conclusions and dissemination. TTB and CB performed the statistical analysis; TTB drafted the initial manuscript and is responsible for the data integrity. All authors contributed to drafting of the manuscript, contributed and agreed on the final manuscript. ÅB is the chief investigator leading protocol development, approvals and dissemination. LN is the guarantor.

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Paper II

ORIGINAL ARTICLE

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Post-fracture Risk Assessment: Target the Centrally Sited Fractures First! A Substudy of NoFRACT

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ABSTRACT

The location of osteoporotic fragility fractures adds crucial information to post-fracture risk estimation. Triaging patients according to fracture site for secondary fracture prevention can therefore be of interest to prioritize patients considering the high imminent fracture risk. The objectives of this cross-sectional study were therefore to explore potential differences between central (vertebral, hip, proximal humerus, pelvis) and peripheral (forearm, ankle, other) fractures. This substudy of the Norwegian Capture the Fracture Initiative (NoFRACT) included 495 women and 119 men ≥50 years with fragility fractures. They had bone mineral density (BMD) of the femoral neck, total hip, and lumbar spine assessed using dual-energy X-ray absorptiometry (DXA), trabecular bone score (TBS) calculated, concomitantly vertebral fracture assessment (VFA) with semiquantitative grading of vertebral fractures (SQ1–SQ3), and a questionnaire concerning risk factors for fractures was answered. Patients with central fractures exhibited lower BMD of the femoral neck (765 versus 827 mg/cm^2), total hip (800 versus 876 mg/cm^2), and lumbar spine (1024 versus 1062 mg/cm^2); lower mean TBS (1.24 versus 1.28); and a higher proportion of SQ1-SQ3 fractures (52.0% versus 27.7%), SQ2–SQ3 fractures (36.8% versus 13.4%), and SQ3 fractures (21.5% versus 2.2%) than patients with peripheral fractures (all $p < 0.05$). All analyses were adjusted for sex, age, and body mass index (BMI); and the analyses of TBS and SQ1–SQ3 fracture prevalence was additionally adjusted for BMD). In conclusion, patients with central fragility fractures revealed lower femoral neck BMD, lower TBS, and higher prevalence of vertebral fractures on VFA than the patients with peripheral fractures. This suggests that patients with central fragility fractures exhibit more severe deterioration of bone structure, translating into a higher risk of subsequent fragility fractures and therefore they should get the highest priority in secondary fracture prevention, although attention to peripheral fractures should still not be diminished. © 2019 American Society for Bone and Mineral Research. © 2019 The Authors. *Journal of Bone and Mineral Research* published by American Society for Bone and Mineral Research.

KEY WORDS: BONE MINERAL DENSITY; OSTEOPOROSIS; TRABECULAR BONE SCORE; VERTEBRAL FRACTURE ASSESSMENT; VERTEBRAL FRACTURES

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Introduction

Fragility fracture is a growing issue worldwide due to longer life expectancies in most populations.[1] The predominant sites of fractures vary with age, and proposed explanations are changes in fall tendency, fall mechanism, and differential loss of cortical and trabecular bone at different stages of aging.[2,3] In clinical assessment after a fragility fracture, the site of fracture adds important information on future fracture risk. In general, a fragility fracture doubles the risk of any subsequent fracture,[4] a hip fracture triples the risk of another hip fracture, and a vertebral fracture increases the risk of subsequent vertebral fracture four to seven times.[4,5] The imminent risk of subsequent fracture is highest the first year after a major osteoporotic fracture (vertebral, hip, distal forearm, proximal humerus) and is more marked in advanced age.[6,7] This constitutes a window of opportunity where antiosteoporotic treatment should be targeted promptly toward patients at highest risk.

The International Osteoporosis Foundation (IOF) recommends assessment of all patients with fragility fractures.[8] Targeting strategies to identify patients at highest risk are warranted to give adequate and timely post-fracture assessment to this large volume of patients. Triaging patients according to fracture types associated with higher or lower expected risk of subsequent fracture could be convenient, especially in areas with limited resources. The major osteoporotic fractures occur at sites that differ with respect to amount and distribution of cortical and trabecular bone. In our Fracture Liaison Service (FLS) clinics, we have observed that patients with fractures at central sites, with abundant trabecular bone (vertebral, hip, proximal humerus, and pelvis), seem to be older and exhibit more pathological features on bone mineral density (BMD), trabecular bone score (TBS), and vertebral fracture assessment (VFA) than patients with fractures at peripheral sites with relatively more cortical bone (forearm, ankle, and other peripheral fractures). This division into central and peripheral fractures diverges from established classifications of fractures such as axial (vertebral, chest, and pelvic) versus appendicular (upper and lower limb) fractures and hip or vertebral versus nonhip nonvertebral fractures. If the clinical observed difference between central and peripheral fractures is significant and persists after adjustment for age and other confounders, this could help to select patients with higher imminent risk of a subsequent fracture first and patients at lower risk second in the FLS model of care.

The objectives of this study were to (i) investigate the risk factors for fractures including BMD, TBS, and proportion of vertebral fracture using VFA in patients with different types of fragility fractures, and (ii) explore the differences between central and peripheral fractures, after adjustment for sex, age, body mass index (BMI), and BMD.

Patients and Methods

Study subjects

NoFRACT is a multicenter study at seven hospitals in Norway with 34976 patients enrolled by January 2019.[9] The objectives of NoFRACT are to investigate the effect on the rate of subsequent fractures of introducing a standardized intervention program consisting of an FLS model of care for identification, assessment, and treatment of osteoporosis in patients with fragility fractures. Eligible for the intervention were women and men aged 50 years or older with any recently diagnosed fragility fracture, except fractures in fingers, toes, and head.[9,10]

This cross-sectional substudy (ClinicalTrials.gov, NCT02608801) of NoFRACT (ClinicalTrials.gov, NCT02536898) included patients at the University Hospital of North Norway, Tromsø, from October 1, 2015, to December 31, 2017, and at the Drammen Hospital from January 1, 2016, to December 31, 2017.[10] During this period, 2682 (>90%) patients above 50 years of age coming to the hospitals with a fragility fracture were identified and offered fracture risk assessment. In most of the elderly inpatients with fractures of the hip, vertebrae, with two or more fragility fractures, or 10-year probability of major osteoporotic fracture ≥20% calculated using the Fracture Risk Assessment Tool (FRAX), the treatment decision was assessed without a dual-energy X-ray absorptiometry (DXA) scan ($n = 1235$). Participants in the substudy were recruited among patients referred to DXA ($n = 1447$) as part of the post-fracture assessment, of whom 58% provided written informed consent ($n = 839$) and 789 had a DXA scan. Of the 789 with a DXA scan, 11 patients had no measurable hips because of metal implants, and one patient was excluded because of poor image quality of the DXA scan. Hence, 777 patients had valid BMD measurement of at least one hip. Of the 785 patients with a DXA scan of the lumbar spine, eight patients were excluded because of less than two evaluable vertebrae. Of the 730 patients who had TBS calculated, 26 patients were excluded due to BMI >37 kg/m^2 (TBS values are not recommended for use in patients with BMI >37 kg/m^2 because of the influence of soft tissue) and 15 patients were excluded because of fractures or anatomical aberrations in two or more vertebrae. Further, only 679 of the patients had lateral thoracolumbar scan for VFA performed. A total of 614 patients had valid BMD measurements of the femoral neck and lumbar spine, VFA, and TBS; 495 women and 119 men. No patients were excluded because of causes known to affect bone metabolism, such as chronic kidney disease ($n = 22$) or use of antiosteoporosis drugs ($n = 39$). The study was approved by The Regional Committee for Medical and Health Research Ethics (REK 2014/2260). To ensure data security a research platform for sensitive data was used.

Variables

The index fractures leading to inclusion were as follows: hip fractures ($n = 41$), vertebral fractures (thoracic and lumbar fractures) ($n = 32$), proximal humerus fractures ($n = 70$), forearm fractures ($n = 247$), ankle fractures ($n = 117$), and other fractures ($n = 107$, including fractures of the pelvis, clavicle, humerus shaft, elbow, hand, distal femur, patella, tibia, and foot). No patients had rib or cervical fractures as index fracture. Vertebral fractures that led to inclusion were diagnosed by X-ray, CT, or MRI, not by VFA. Fracture cases were categorized into groups of index fractures. Based on location and relative proportions of trabecular and cortical bone, we chose to divide fractures into: central fractures (vertebra, hip, proximal humerus, and pelvis) and peripheral fractures (humerus shaft, clavicle, elbow, forearm, hand, distal femur, patella, tibia, ankle, and foot). We also divided the patients into the established groups of axial (spine, chest, and pelvic) versus appendicular (upper or lower limb) fractures. In addition, information on number of previous fractures after the age of 50 years, number of falls during the last 12 months before inclusion, parental history of hip fractures, use of tobacco, diagnosis of rheumatoid arthritis, and use of glucocorticoids was collected through a questionnaire.

Height and weight were measured. BMI was calculated as weight (kg) per square meter height. BMD was measured at the femoral neck and total hip bilaterally and lumbar spine (L_1–L_4)

using DXA (Prodigy Pro; GE Lunar, Madison, WI, USA) in Tromsø and iDXA (Prodigy Pro; GE Lunar, Madison, WI, USA) in Drammen. Phantom quality assurance (QA) of the DXA equipment was performed daily. Lumbar vertebrae with fracture were excluded. BMD *T*-scores were calculated using the Third National Health and Nutrition Examination Survey reference data for white females aged 20 to 29 years.[11] Osteoporosis was defined as femoral neck BMD *T*-score of −2.5 or less, and osteopenia as femoral neck BMD *T*-score between −2.5 and −1.0 according to the diagnosis criteria of the World Health Organization.[12]

TBS was calculated from the lumbar spine (L_1–L_4) DXA scans using TBS iNsight™ software (Medimaps, Geneva, Switzerland) version 3.0.1. Fractured vertebrae were omitted. The European (Medimaps) reference population was used for both sexes. The TBS values were divided into three groups according to estimated fracture risk: high TBS ≥1.31 (low fracture risk), TBS between 1.23 and 1.31 (intermediate fracture risk), and low TBS ≤ 1.23 (high fracture risk).[13]

Images of the lateral thoracolumbar spine (T_4–L_4) were obtained and VFA of the fracture severity was performed using the semiquantitative (SQ) vertebral deformity scoring method by Genant.[10,14] An SQ0 (<20% height loss) was considered as a nonfractured vertebra, SQ1 (20% to 25% height loss) as a mild fracture, SQ2 (25% to 40% height loss) as a moderate fracture, and SQ3 (≥40% height loss) as a severe fracture. Presence of one or more SQ1, SQ2, or SQ3 fractures was termed SQ1–SQ3 fracture and presence of one or more SQ2 or SQ3 fractures was termed SQ2–SQ3 fracture. Patients were also categorized by presence of at least one SQ3 fracture (yes versus no) as a measure of severe deteriorated microarchitecture in trabecular bone. The interobserver agreement of SQ1–SQ3 fractures between two experienced clinicians has shown a κ of 0.84 (95% confidence interval, 0.70 to 0.98).[10]

Statistical analyses

The mean ± SD for the continuous variables and *n* (%) for categorical variables of the characteristics are presented for each of the fracture groups. Continuous variables were checked for normality using quantile-quantile (QQ) plot. The patients were stratified by type of index fracture to show the proportion of patients with osteoporosis at femoral neck, low TBS (TBS ≤ 1.23), and SQ1–SQ3 in the fracture groups. Further, the patients were stratified by age to show the distribution of osteoporosis, osteopenia, and normal BMD at the femoral neck by age and type of fracture. Scatterplot with regression lines of femoral neck BMD, TBS, and proportion of vertebral fractures by 10-year age groups, and vertical lines for the mean age of patients with each type of fractures are shown. Multiple linear regression analyses were used to investigate differences in continuous variables between types of fracture after adjustment for age and sex. Each group was compared to the hip fracture group. This reference group was chosen because fracture of the hip is considered the most serious. Differences between patients with central versus peripheral fractures and axial versus appendicular fractures were assessed using linear regression analyses for continuous variables and Pearson chi-squared test or Fisher's exact test for dichotomous variables. The comparisons of risk factors for fracture between the fracture groups are presented in three models: unadjusted; after adjustment for sex, BMI, and femoral neck BMD; and after an additional adjustment for age. In sensitivity analyses, we compared central fractures versus forearm fractures, central fractures versus peripheral fractures (after exclusion of other fractures), and central (after exclusion of vertebral fractures) versus peripheral fractures, which are shown in Tables S1–S3. To investigate whether the results differed by sex the analyses of central versus peripheral fractures were replicated for women and men separately. Area under the receiver operating characteristic curve (AUC) analyses were performed to explore which of the bone phenotypes was the best to discriminate between the patients with central versus peripheral fractures. Analyses were performed using Stata v15 (version 15; Stata Corporation, Inc., College Station, TX, USA).

Results

Patient characteristics according to fracture types

The majority of the patients were women and 59% of the patients had a fracture of the forearm or ankle (Table 1). Patients with forearm, ankle, and other fractures were younger than those with hip fractures (all $p < 0.01$). BMD at the femoral neck, total hip, and the site with lowest *T*-score was higher in patients with proximal humerus, forearm, ankle, and other types of fractures than those with hip fractures (all $p < 0.05$). The proportion of patients with osteoporosis at the femoral neck was highest in patients with hip fracture (Table 1, Figs. 1 and 2). Mean TBS was higher in patients with other fractures than those with hip fracture (Table 1). BMD and TBS decreased with age, whereas the proportion of patients with SQ1–SQ3 fractures increased (Fig. 3).

Patients with central fractures versus peripheral fractures

One in four patients had sustained a central index fracture (Table 2). Patients with central fractures were older (70.4 versus 64.4 years, $p < 0.001$) exhibited lower BMD at femoral neck, total hip, and at the site with lowest *T*-score (all $p < 0.001$). Those with central fractures also had lower mean TBS (1.24 versus 1.28) and a higher proportion of SQ1–SQ3 fractures (52.0% versus 27.7%), SQ2–SQ3 fractures (36.8% versus 13.4%), and SQ3 fractures (21.5% versus 2.2%) than patients with peripheral fractures after adjustment for sex, BMI, and femoral neck BMD (all $p < 0.05$). These differences in femoral neck BMD, TBS, and proportion of patients with SQ fractures between the central and peripheral fracture groups remained significant after additional adjustment for age. Patients with central fractures were older, exhibited lower BMD at femoral neck and total hip, and a higher proportion of SQ1–SQ3, SQ2–SQ3, and SQ3 fractures than patients with forearm fractures (Table S1) and patients with forearm or ankle fractures (Table S2) (all $p < 0.01$). When patients with vertebral index fractures were excluded from the analyses, patients with central fractures were still older (69.9 versus 64.4 years), exhibited lower BMD at femoral neck and total hip, and a higher proportion of SQ3 fractures (12.5% versus 2.2%) than patients with peripheral fractures (all $p < 0.01$) (Table S3). However, there was no difference in TBS or proportion of SQ1–SQ3 and SQ2–SQ3 fractures between patients with central and peripheral fractures after exclusion of patients with vertebral index fractures. In sex-stratified analyses, we found the same results in the women as in the total cohort, except for lower TBS in those with central versus peripheral fractures after adjustment for age and BMI ($p = 0.003$), but not after additional adjustment for femoral neck BMD ($p = 0.066$) (data not shown). In men, we found no significant difference in femoral neck BMD, TBS, or proportion of SQ1–SQ3 fractures between those with central versus peripheral

Table 1. Characteristics of Patients by Type of Fracture and Compared to Hip Fracture as the Reference Group

Characteristic	Hip	Vertebral	Humerus	Forearm	Ankle	Other
Total patients	41 (6.7)	32 (5.2)	70 (11.4)	247 (40.2)	117 (19.1)	107 (17.4)
Women	27 (65.9)	26 (81.3)	62 (88.6)	218 (88.7)	85 (72.6)	77 (72.0)
Age (years)	70.4 ± 8.3	72.4 ± 6.5	68.7 ± 8.3	64.2 ± 8.1[3]	65.4 ± 8.8[2]	64.6 ± 8.8[3]
BMI (kg/m^2)	24.8 ± 3.2	28.9 ± 4.9	26.9 ± 4.4[2]	26.1 ± 3.8	27.6 ± 3.9[3]	26.3 ± 4.1
Prior fracture	16/32 (50.0)	11/21 (52.4)	29/58 (50.0)	69/189 (36.5)	32/91 (35.2)	41/86 (47.7)
Smoking	1/30 (3.3)	3/23 (13.0)	10/60 (16.7)	23/193 (12.0)	15/98 (15.3)	16/95 (16.8)
Parental hip fracture	7/26 (26.9)	7/18 (38.9)	16/50 (32.0)	43/169 (25.4)	9/78 (11.5)	14/63 (18.2)
Glucocorticoid use	1/31 (3.2)	3/23 (13.0)	3/58 (5.2)	13/197 (6.6)	1/99 (1.0)	6/97 (6.2)
Rheumatoid arthritis	2/31 (6.5)	1/24 (4.2)	4/59 (6.8)	8/197 (4.0)	4/99 (4.0)	2/95 (2.1)
Femoral neck BMD (mg/cm^2)	732 ± 127	757 ± 117	797 ± 106[3]	811 ± 110[3]	846 ± 113[3]	829 ± 122[3]
Femoral neck BMD *T*-score	−2.2 ± 0.9	−2.0 ± 0.9	−1.7 ± 0.8[3]	−1.6 ± 0.8[3]	−1.4 ± 0.8[3]	−1.5 ± 0.9[3]
Normal	4 (9.8)	4 (12.5)	10 (14.3)	44 (17.8)	34 (29.1)	27 (25.2)
Osteopenia	19 (46.3)	19 (59.4)	51 (72.9)	173 (70.0)	75 (64.1)	69 (64.5)
Osteoporosis	18 (43.9)	9 (28.1)	9 (12.9)	30 (12.1)	8 (6.8)[1]	11 (10.3)
Total hip BMD (mg/cm^2)	762 ± 142	788 ± 129	836 ± 117[3]	853 ± 116[3]	907 ± 135[3]	885 ± 146[3]
Total hip BMD *T*-score	−1.9 ± 1.1	−1.8 ± 1.0	−1.4 ± 0.9[3]	−1.2 ± 0.9[3]	−0.8 ± 1.1[3]	−1.0 ± 1.2[3]
Lumbar spine BMD (mg/cm^2)	1060 ± 207	998 ± 183	1014 ± 156	1031 ± 170	1099 ± 171	1091 ± 179
Lumbar spine BMD *T*-score	−1.1 ± 1.7	−1.6 ± 1.5	−1.5 ± 1.3	−1.3 ± 1.4	−0.8 ± 1.4	−0.8 ± 1.4
Lowest BMD *T*-score all sites	−2.4 ± 1.0	−2.5 ± 0.9	−2.1 ± 0.8[1]	−2.0 ± 0.8[1]	−1.7 ± 0.9[3]	−1.8 ± 1.0[2]
Normal	4 (9.8)	2 (6.3)	5 (7.1)	25 (10.1)	22 (18.8)	18 (16.8)
Osteopenia	17 (41.5)	15 (46.9)	41 (58.6)	154 (62.3)	76 (65.0)	65 (60.7)
Osteoporosis	20 (48.8)	15 (46.9)	24 (34.3)	68 (27.6)	19 (16.2)[1]	24 (22.4)
Trabecular bone score	1.25 ± 0.11	1.21 ± 0.10	1.25 ± 0.10	1.28 ± 0.09	1.28 ± 0.11	1.31 ± 0.11[1]
≥1.31	14 (34.1)	5 (15.6)	20 (28.6)	88 (35.6)	49 (41.9)	52 (48.6)
1.23–1.31	12 (29.3)	11 (34.4)	19 (27.1)	86 (34.8)	26 (22.2)	28 (26.2)
≤1.23	15 (36.6)	16 (50.0)	31 (44.3)	73 (29.6)	42 (35.9)	27 (25.2)
SQ1–SQ3 fracture	17 (41.5)	28 (87.5)[3]	28 (40.6)	64 (25.9)	31 (26.5)	39 (36.5)
SQ2–SQ3 fracture	12 (29.3)	26 (81.3)[3]	13 (18.6)	29 (11.7)[2]	16 (13.7)[1]	22 (20.6)
≥1 SQ3 fracture	4 (9.8)	18 (56.3)[3]	7 (10.0)	4 (1.6)[1]	4 (3.4)	6 (5.6)

Values are mean ± SD or *n* (%).

BMD = bone mineral density; BMI = body mass index; SQ = semiquantitative score.

[1] $p < 0.05$, adjusted for sex and age, except the analyses of age, which was only adjusted for sex.

[2] $p < 0.01$, adjusted for sex and age, except the analyses of age, which was only adjusted for sex.

[3] $p < 0.001$, adjusted for sex and age, except the analyses of age, which was only adjusted for sex.

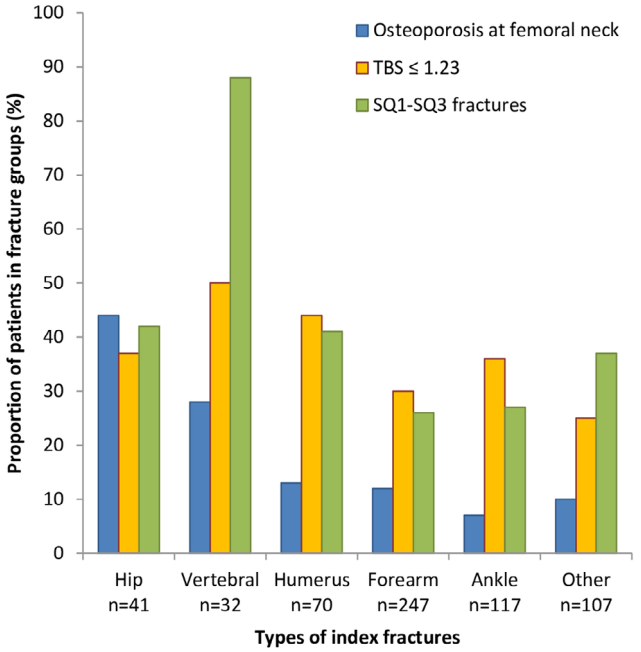

Fig. 1. Proportions of patients with osteoporosis at the femoral neck, low TBS and vertebral fractures (SQ1–SQ3) on vertebral fracture assessment by type of fracture. TBS = trabecular bone score.

fractures after adjusting for age and BMI ($p > 0.05$) (data not shown).

For discrimination of patients with central versus peripheral fractures, the AUC for femoral neck BMD, TBS, and SQ1–SQ3 fractures was 0.644, 0.624, and 0.623, respectively. Adding TBS to femoral neck BMD increased the AUC from 0.644 to 0.663 ($p = 0.300$). Adding SQ1–SQ3 fractures to femoral neck BMD increased the AUC to 0.684 ($p = 0.002$).

Patients with axial fractures versus appendicular fractures

One in 15 patients had an axial index fracture (Table 3). Patients with axial fractures were older (73.2 versus 65.3 years) and exhibited lower BMD at the femoral neck, total hip, and the site with lowest *T*-score after adjustment for age, sex, and BMI (all $p < 0.001$). Those with axial fractures also had lower mean TBS (1.21 versus 1.28) and a higher proportion of SQ1–SQ3 fractures (82.9% versus 30.2%), SQ2–SQ3 fractures (75.9% versus 15.2%), and SQ3 fractures (68.3% versus 8.7%) than those with appendicular fractures after adjustment for sex, BMI, and femoral neck BMD (all $p < 0.05$). All these differences remained statistically significant after additional adjustment for age.

Discussion

In this cohort of subjects with fractures, those with centrally and axially located fractures exhibited lower BMD, lower TBS, and exhibited more SQ1–SQ3, SQ2–SQ3, and SQ3 fractures than those with peripheral and appendicular fractures. These differences remained significant after adjustment for sex, age, BMI, and femoral neck BMD, which supports the notion that intrinsic skeletal properties and localization of fractures are connected.

We propose grouping fragility fractures into central versus peripheral fractures. This emerges from a clinical observation of similarities in patients with these types of fractures, which also is in accordance with the relative proportions of trabecular and cortical bone at these sites. This grouping is a mélange of existing classifications of fractures. The group of central fractures includes both axial and hip/vertebral fractures, in addition to proximal humeral fractures. The group of peripheral fractures consists of mainly forearm and ankle fractures, but also other fractures of the limbs from the diaphysis and distally of the humerus and femur. Patients with central fractures exhibited lower BMD including femoral neck, lower TBS, and a higher prevalence of vertebral fractures, all associated with increased fracture risk,[15–17] than did patients with peripheral fractures.

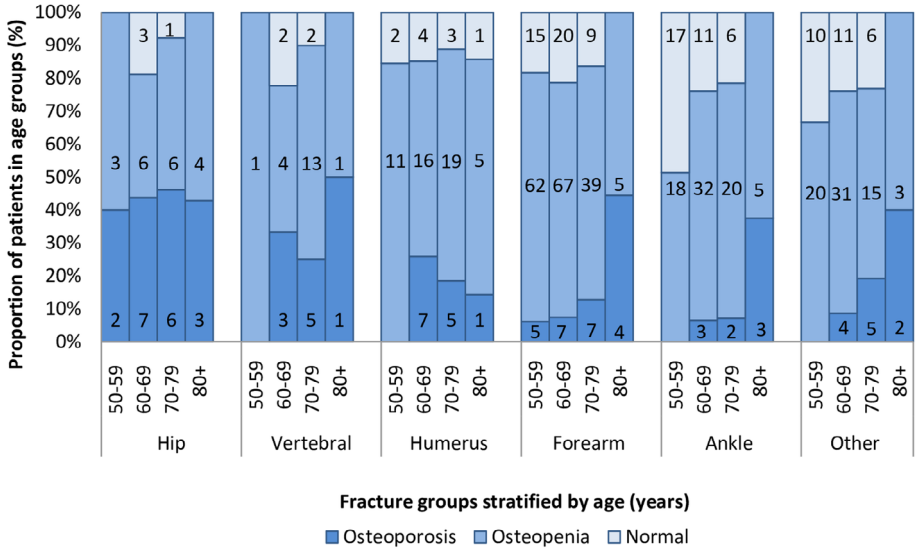

Fig. 2. Proportion and number of patients with osteoporosis, osteopenia, and normal bone mineral density at the femoral neck stratified by types of fracture and in 10-year age groups. Number of patients are shown within each column.

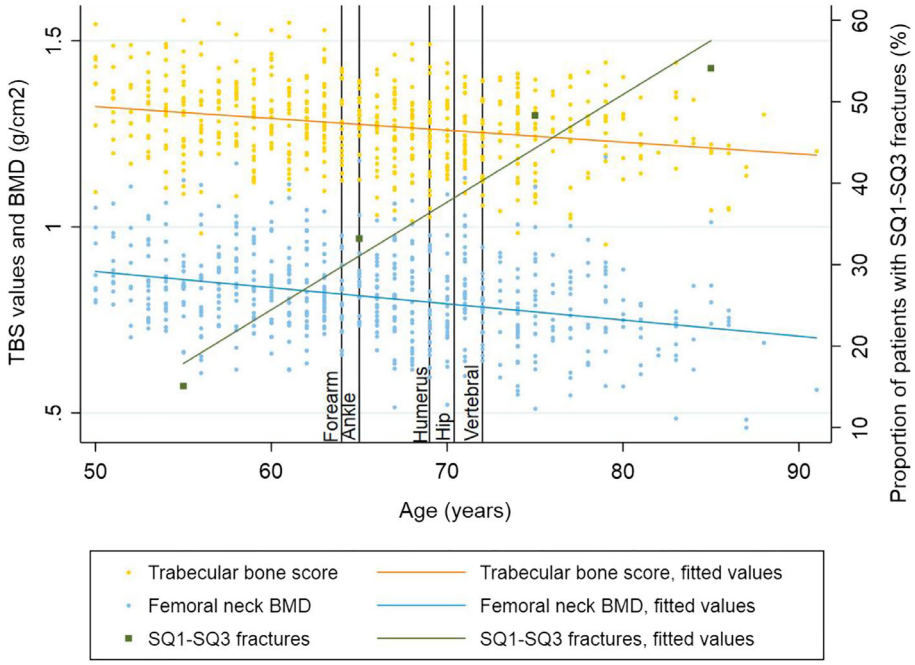

Fig. 3. Fitted lines of TBS and femoral neck BMD and prevalence of SQ1–SQ3 fractures on vertebral fracture assessment in relation to age. BMD = bone mineral density; TBS = trabecular bone score.

Although the difference in TBS and SQ1–SQ3 and SQ2–SQ3 fractures was no longer significant after removing patients with vertebral index fractures, the difference in femoral neck BMD and SQ3 fractures remained. Dividing patients into high-risk and low-risk groups is meaningful, to identify and prioritize the patients at highest risk first for post-fracture assessment in this large volume of patients. These differences were also observed, and also even more marked, when axial fractures were compared to appendicular fractures. Despite this, division into axial and appendicular does not seem to be useful for this purpose, because the group of axial fractures only accounts for 7% of the patients and lacks serious types of fractures such as hip and humerus fractures.

The central fractures are sited in the axial and proximal appendicular part of the skeleton, which encompasses a large proportion of trabecular bone, in most areas exceeding 50%. This was corroborated by our findings of lower TBS in patients with central fractures than in patients with peripheral fractures. Mean TBS, which is a texture index reflecting bone microarchitecture, has been shown to be lower in patients who have sustained fragility fractures compared to fracture-free controls[18,19] and to be lower in patients with than without vertebral fractures on VFA.[10,20] More than one-half of the patients with central fractures in our study had prevalent vertebral fractures on VFA, almost twice the prevalence in the patients with peripheral fractures. This was obviously enhanced by the group of vertebral index fractures. After exclusion of the patients with vertebral fractures, patients with central fractures still exhibited a higher proportion of SQ3 fractures. VFA provides information on trabecular bone strength, because severity of vertebral compressions reflect deterioration of trabecular bone microarchitecture.[21] The patients with central fractures also exhibited lower femoral neck BMD than those with peripheral fractures. Femoral neck BMD can be considered as a proxy of cortical bone strength, because 75% of the bone volume at this site is cortical.[3] Hence, in patients with central fractures, *both* trabecular and cortical bone strength are reduced compared to those with peripheral fractures. Cortical bone architecture is important for fracture propensity, as shown in the Tromsø study.[22] A thinner cortex and increased cortical porosity at the proximal femur were associated with increased risk of fractures.[23] The importance of coexisting cortical and trabecular deterioration for fracture propensity has recently been demonstrated using CT at distal forearm in women.[24,25] Lower femoral neck BMD, lower TBS, and more prevalent vertebral fractures on VFA express lower total bone strength, which in this study is associated with serious fractures like hip and vertebral fractures, fractures that previously have been shown to be associated with increased morbidity and mortality.[26–29]

Prospective studies have shown that low BMD measured at central,[17] as well as peripheral sites,[30,31] predicts any type of fracture. TBS predicts major osteoporotic, clinical vertebral and hip fractures,[19] and vertebral fractures predict new vertebral and nonvertebral fractures.[5,32] We therefore interpret that patients with central fractures, who have lower BMD, lower TBS, and more prevalent vertebral fractures, have a higher risk of future fractures at all sites, including higher imminent fracture risk, than patients with peripheral fractures. However, a peripheral fracture can be an early sign of bone fragility, and with advancing age and bone loss, these patients are expected to have an increased risk of central fractures. Therefore, these patients are also important to assess to prevent future serious major fractures, and the attention to peripheral fractures should not be diminished.

One additional, possible mechanism explaining the differences observed in this study might be falls. In particular in

Table 2. Characteristics of Patients With Central Fractures and Peripheral Fractures

Characteristic	Central fractures	Peripheral fractures	p^1	p^2	p^3
Total patients	152 (24.8)	462 (75.2)			
Women	121 (79.6)	374 (81.0)	0.716	0.079	0.408
Age (years)	70.4 ± 8.1	64.4 ± 8.3	<0.001	<0.001	0.001
BMI (kg/m^2)	26.0 ± 4.2	26.7 ± 4.0	0.125	0.737	0.787
Prior fracture	62/118 (52.5)	136/359 (37.9)	0.005	0.055	0.384
Smoking	15/121 (12.4)	53/377 (14.1)	0.643	0.616	0.925
Falls in the last year	1.3 ± 0.8	1.3 ± 0.8	0.475	0.405	0.443
Parental hip fracture	30/99 (30.3)	66/319 (20.7)	0.047	0.111	0.029
Glucocorticoid use	7/120 (5.8)	20/385 (5.2)	0.786	0.853	0.896
Rheumatoid arthritis	7/122 (5.7)	14/383 (3.7)	0.316	0.288	0.339
Femoral neck BMD (mg/cm^2)	765 ± 118	827 ± 113	<0.001	<0.001	<0.001
Femoral neck BMD *T*-score	−2.0 ± 0.9	−1.5 ± 0.9	<0.001	<0.001	<0.001
Normal	18 (11.8)	105 (22.7)			
Osteopenia	95 (62.5)	311 (67.3)			
Osteoporosis	39 (25.7)	46 (10.0)			
Total hip BMD (mg/cm^2)	800 ± 131	876 ± 129	<0.001	<0.001	<0.001
Total hip BMD *T*-score	−1.7 ± 1.0	−1.0 ± 1.1	<0.001	<0.001	<0.001
Lumbar spine BMD (mg/cm^2)	1024 ± 180	1062 ± 174	0.022	0.030	0.048
Lumbar spine BMD *T*-score	−1.4 ± 1.5	−1.1 ± 1.4	0.022	0.030	0.051
Lowest BMD *T*-score all sites	−2.3 ± 0.9	−1.9 ± 0.9	<0.001	<0.001	0.001
Normal	11 (7.2)	65 (14.1)			
Osteopenia	77 (50.7)	291 (63.0)			
Osteoporosis	64 (42.1)	106 (22.9)			
Trabecular bone score	1.24 ± 0.10	1.28 ± 0.10	<0.001	0.003	0.034
≥1.31	40 (26.3)	188 (22.7)			
1.23–1.31	44 (28.9)	138 (29.9)			
≤1.23	68 (44.8)	136 (29.4)			
SQ1–SQ3 fractures	79 (52.0)	128 (27.7)	<0.001	<0.001	<0.001
SQ2–SQ3 fractures	56 (36.8)	62 (13.4)	<0.001	<0.001	<0.001
≥1 SQ3 fracture	32 (21.5)	10 (2.2)	<0.001	<0.001	<0.001

Values are mean ± SD or *n* (%). Analysis of age was not adjusted for age, analysis of sex was not adjusted for sex, analysis of BMI was not adjusted for BMI, and analysis of BMD was not adjusted for femoral neck BMD.

BMD = bone mineral density; BMI = body mass index; SQ = semiquantitative score.

[1] Unadjusted.

[2] Adjusted for sex, BMI, and femoral neck BMD.

[3] Adjusted for age, sex, BMI, and femoral neck BMD.

relation to hip fractures, but also other peripheral fractures, falls have been invoked to explain fractures in subjects with non-osteoporotic BMD. We found no differences, however, in number of falls during the last 12 months prior to inclusion between patients with central and peripheral fractures (Table 2). Hence, propensity for falls did not influence the type of fracture sustained in this study. We had no detailed information on the mechanism of the falls, which is a possible limitation. There were no differences in number of previous fractures, smoking habits, use of glucocorticoids, or rheumatoid arthritis between the groups. However, more patients with central fractures reported that they had parents with a hip fracture than those with peripheral fractures. After adjustment for covariates, the remaining differences between the patients with central versus peripheral fractures were the intrinsic skeletal properties, assessed using BMD, TBS, and VFA.

To our knowledge, this study is the first to classify patients with fragility fractures into central and peripheral groups. That these two groups of patients differ is intuitive, but showing this and quantifying it with data is novel. However, the study has some limitations. First, only patients in need of a DXA examination who were healthy enough to undergo follow-up were invited to this substudy. This resulted in a selection of healthy patients, with a relatively small proportion of hip fractures. Further, some fracture groups were small. We therefore combined women and men to gain statistical power. The number of men was small and therefore some of our conclusions may not be applicable for men. Finally, the study lacks a control group, and we only measured BMD at central sites. A peripheral measurement could have been of interest to explore whether patients with peripheral fractures would exhibit lower BMD at a peripheral site than patients with central fractures.

In conclusion, patients with fractures at central sites exhibited lower BMD at the femoral neck, total hip, and the site with lowest *T*-score, lower TBS, and higher prevalence of vertebral fractures on VFA than patients with peripheral fractures. These findings indicate that bone loss and deterioration of cortical and trabecular bone structure are important determinants for fractures at these sites. Hence, patients with central fractures are expected to have a higher risk of subsequent fractures. All patients with fragility fractures require secondary fracture assessment, but we propose that patients with central fractures should get the highest priority and be assessed first. This does not imply that the attention to peripheral fractures should be reduced. In recent years, however, new techniques focusing on trabecular bone such as TBS and VFA have emerged, but they are less predictive

Table 3. Characteristics of Patients With Axial Fractures and Appendicular Fractures

Characteristic	Axial fractures	Appendicular fractures	p^1	p^2	p^3
Total patients	41 (6.7)	573 (93.3)			
Women	32 (78.1)	463 (80.8)	0.666	0.171	0.515
Age (years)	73.2 ± 6.7	65.3 ± 8.5	<0.001	<0.001	<0.001
BMI (kg/m^2)	25.7 ± 4.5	26.5 ± 4.0	0.224	0.966	0.990
Prior fracture	17/28 (60.7)	181/449 (40.3)	0.034	0.047	0.445
Smoking	4/31 (12.9)	64/467 (13.7)	0.900	0.901	0.729
Falls in the last year	1.1 ± 0.8	1.3 ± 0.7	0.124	0.099	0.108
Parental hip fracture	7/23 (30.4)	89/395 (22.5)	0.381	0.536	0.303
Glucocorticoid use	3/31 (9.7)	24/474 (5.1)	0.269	0.292	0.306
Rheumatoid arthritis	1/32 (3.1)	20/473 (4.2)	0.893	0.771	0.571
Femoral neck BMD (mg/cm^2)	744 ± 116	816 ± 115	<0.001	<0.001	0.030
Femoral neck BMD *T*-score	−2.1 ± 0.8	−1.6 ± 0.8	<0.001	<0.001	0.031
Normal	4 (9.8)	119 (20.8)			
Osteopenia	25 (61.0)	381 (66.5)			
Osteoporosis	12 (29.2)	73 (12.7)			
Total hip BMD (mg/cm^2)	775 ± 130	863 ± 131	<0.001	<0.001	0.007
Total hip BMD *T*-score	−1.9 ± 1.0	−1.1 ± 1.0	<0.001	<0.001	0.006
Lumbar spine BMD (mg/cm^2)	1007 ± 188	1056 ± 175	0.087	0.095	0.134
Lumbar spine BMD *T*-score	−1.5 ± 1.5	−1.1 ± 1.4	0.079	0.087	0.128
Lowest BMD *T*-score all sites	−2.5 ± 0.9	−1.9 ± 0.9	<0.001	<0.001	0.015
Normal	2 (4.9)	74 (12.9)			
Osteopenia	19 (46.3)	349 (60.9)			
Osteoporosis	20 (48.8)	150 (20.2)			
Trabecular bone score	1.21 ± 0.10	1.28 ± 0.10	<0.001	<0.001	0.040
≥1.31	6 (14.6)	222 (38.7)			
1.23–1.31	13 (31.7)	169 (29.5)			
≤1.23	22 (53.7)	182 (31.8)			
SQ1–SQ3 fractures	34 (82.9)	173 (30.2)	<0.001	<0.001	<0.001
SQ2–SQ3 fractures	31 (75.6)	87 (15.2)	<0.001	<0.001	<0.001
≥1 SQ3 fracture	21 (51.2)	21 (3.7)	<0.001	<0.001	<0.001

Values are mean ± SD or *n* (%). Analysis of age was not adjusted for age, analysis of sex was not adjusted for sex, analysis of BMI was not adjusted for BMI, and analysis of BMD was not adjusted for femoral neck BMD.

BMD = bone mineral density; BMI = body mass index; SQ = semiquantitative score.

[1] Unadjusted.

[2] Adjusted for sex, BMI, and femoral neck BMD.

[3] Adjusted for age, sex, BMI, and femoral neck BMD.

for peripheral fractures. New modalities focusing on cortical bone structure, therefore, remain an unmet medical need.

Disclosures

LBS has received speaker honorarium from Eli Lilly. MBS has received speaker fees from Eli Lilly, Amgen, UCB, and Takeda. WF has received speaker fees from Ortomedic AS and Zimmer Biomet. JMS has received grants for educational activities from BSN Medical. LN has received speaker fees from Novartis, Eli Lilly, and Ortomedic AS. FF has received grants for educational activities from Eli Lilly, Amgen, and Takeda. EFE has received speaker fees from Novartis, Eli Lilly, Amgen, MSD, EffRx, IDS, and Shire. The remaining authors have no conflicts of interest to report.

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Authors' roles

TTB, ÅB, and EFE led the design of this substudy. TTB, ÅB, LBS, TKO, and TB designed the questionnaires. TTB, ÅB, and CA led the patient involvement and data collection. All authors contributed to methodological decisions, data interpretation, conclusions, and dissemination. TTB and CB performed the statistical analysis; TTB drafted the initial manuscript and is responsible for the data integrity. All authors contributed to drafting of the manuscript, contributed, and approved the final manuscript. ÅB is the chief investigator leading protocol development, approvals, and dissemination. LN is the guarantor.

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Paper III

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ORIGINAL ARTICLE

Determinants of trabecular bone score and prevalent vertebral fractures in women with fragility fractures: a cross-sectional sub-study of NoFRACT

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Abstract

Summary Determinants of trabecular bone score (TBS) and vertebral fractures assessed semiquantitatively (SQ1–SQ3) were studied in 496 women with fragility fractures. TBS was associated with age, parental hip fracture, alcohol intake and BMD, not SQ1–SQ3 fractures. SQ1–SQ3 fractures were associated with age, prior fractures, and lumbar spine BMD, but not TBS.

Introduction Trabecular bone score (TBS) and vertebral fractures assessed by semiquantitative method (SQ1–SQ3) seem to reflect different aspects of bone strength. We therefore sought to explore the determinants of and the associations between TBS and SQ1–SQ3 fractures.

Methods This cross-sectional sub-study of the Norwegian Capture the Fracture Initiative included 496 women aged ≥ 50 years with fragility fractures. All responded to a questionnaire about risk factors for fracture, had bone mineral density (BMD) of femoral neck and/or lumbar spine assessed, TBS calculated, and 423 had SQ1–SQ3 fracture assessed.

Results Mean (SD) age was 65.6 years (8.6), mean TBS 1.27 (0.10), and 33.3% exhibited SQ1–SQ3 fractures. In multiple variable analysis, higher age ($\beta_{\text{per SD}} = -0.26$, 95% CI: − 0.36,− 0.15), parental hip fracture (β = − 0.29, 95% CI: − 0.54,− 0.05), and daily alcohol intake (β = − 0.43, 95% CI − 0.79, − 0.08) were associated with lower TBS. Higher BMD of femoral neck ($\beta_{\text{per SD}} = 0.34$, 95% CI 0.25–0.43) and lumbar spine ($\beta_{\text{per SD}} = 0.40$, 95% CI 0.31–0.48) were associated with higher TBS. In multivariable logistic regression analyses, age ($OR_{\text{per SD}} = 1.94$, 95% CI 1.51–2.46) and prior fragility fractures (OR = 1.71, 95% CI 1.09–2.71) were positively associated with SQ1–SQ3 fractures, while lumbar spine BMD ($OR_{\text{per SD}} = 0.75$ 95% CI 0.60–

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0.95) was negatively associated with SQ1–SQ3 fractures. No association between TBS and SQ1–SQ3 fractures was found.
Conclusion Since TBS and SQ1–SQ3 fractures were not associated, they may act as independent risk factors, justifying the use of both in post-fracture risk assessment.

Keywords Bone mineral density · Fracture risk · Osteoporosis · Trabecular bone score · Vertebral fracture assessment · Vertebral fractures

Introduction

In recent years, trabecular bone score (TBS) and vertebral fracture assessment (VFA) have become established methods in clinical use, providing supplemental information on bone strength and future fracture risk [1–3]. Identification of the determinants of these indices is important for further understanding the pathophysiology of fracture risk and for identification of modifiable factors to prevent future fractures.

TBS is a grey-level textural index of trabecular bone microarchitecture obtained from dual-energy absorptiometry (DXA) images of the lumbar spine [4]. It is, however, still subject to discussion, which bone properties TBS actually reflects [5]. TBS predicts fragility fractures independently of bone mineral density (BMD) [2, 6–8]. The use of TBS for adjustment of 10-year probability of a hip or other major osteoporotic fracture (MOF) calculated by the Fracture Risk Assessment Tool (FRAX) is endorsed [9]. The retrospective Manitoba study is the largest study on determinants of TBS (n = 29,407 women)[10]. They found that TBS was negatively associated with glucocorticoid use, prior major fracture, rheumatoid arthritis, chronic obstructive pulmonary disease, high alcohol intake and higher body mass index (BMI) and positively associated with femoral neck and lumbar spine BMD, and 7–11% of the variation in TBS was explained by BMD [10]. Genetic factors explained approximately 45% of the variance in TBS in healthy Vietnamese subjects, whereas sex, age, and height accounted for about 28% of the total variance in TBS [11].

The presence of a vertebral fracture doubles the risk of subsequent fracture at any given BMD [12]. VFA of lateral spine x-rays is therefore recommended as a part of the post-fracture risk assessment [13]. With higher resolution and image quality of modern DXA equipment, VFA of spine images obtained by DXA has become easily available and provides reliable information on vertebral fracture status in the thoracolumbar spine (T4–L4) at a much lower radiation dose compared to conventional lateral spine x-rays. Determinants as age, BMD, height loss, and prior non-vertebral fractures are associated with prevalent vertebral fractures in a large population-based cohort study [14]. In the Rotterdam Study, incident vertebral fractures were reported to be strongly associated with prevalent vertebral fractures, early menopause, current smoking, use of walking aids, and low BMD [15]. In addition, the population-based European Prospective Osteoporosis Study (EPOS) showed that low BMD, low BMI, and late menarche were associated with higher incidence of vertebral fractures while use of hormonal replacement therapy (HRT) was protective [16]. No associations between lifestyle factors such as smoking, alcohol intake, physical activity, or milk consumption and incident vertebral fracture were found in that study. A heritability of vertebral fractures (vertebral height reduction > 25%) of more than 43% has been demonstrated [17].

Studies on the association between TBS and vertebral fractures diverge. Low TBS has been shown to be associated with a higher prevalence of vertebral fractures on VFA in women [18, 19], but there are also studies contradicting this notion [20]. In the prospective Manitoba study, TBS was associated with incident vertebral fractures in women but not in men [21]. Moreover, TBS was not associated with incident vertebral fractures in the men in the MrOs study [22]. In a previous publication of results from this sub-study of Norwegian Capture the Fracture Initiative (NoFRACT), we reported that more than half of the patients who had sustained a fragility fracture exhibited low TBS (≤ 1.23), prevalent fracture on VFA or both [23]. Only 14% of these patients exhibited osteoporosis at the femoral neck, which increased to 28% when using the site with lowest BMD T-score. In the patients with osteopenia at the femoral neck, 34% exhibited low TBS, 33% vertebral fracture on VFA, but only 13% exhibited both low TBS and prevalent vertebral fracture. This is suggesting that TBS and VFA captured different aspects of bone strength. To better understand the potential pathophysiology underlying this diversity, identification of the determinants of both traits in the same cohort is of interest. Keeping in mind that heritability is a major determinant, investigation of clinical phenotypes and modifiable environmental risk factors may enable identification and treatment of individuals at risk. To our knowledge, this has not been studied in individuals with fractures. The objectives of this study were therefore (i) to explore the determinants of TBS and prevalent vertebral fractures on VFA, (ii) to explore whether prevalent vertebral fractures are determinants of TBS, and (iii) to explore whether TBS is a determinant of vertebral fractures in a cohort of women with fragility fractures.

Material and methods

Study subjects

NoFRACT is a multicenter study at seven hospitals in Norway with 34,976 persons with fragility fractures enrolled by Jan 2019 [24]. The main aim is to investigate the effect of introducing a standardized intervention program consisting of a Fracture Liaison Service model of care for identification, assessment, and treatment of osteoporosis in patients with fragility fractures on the rate of subsequent fractures. Both women and men aged 50 years and older, who have recently sustained a clinical fragility fracture, are eligible to the intervention, with the exception of patients with fracture in fingers, toes, skull, and face.

This cross-sectional sub-study (NCT02608801) of NoFRACT (NCT02536898) included patients at the University Hospital of North Norway, Tromsø, from 1 Oct 2015 to 31 Dec 2017 and at Drammen Hospital in the south-eastern part of Norway from 1 Jan 2016 to 31 Dec 2017 [23, 25]. Of all patients of 50 years of age and above, attending to these hospitals with a fragility fracture, more than 90% (n = 2682) were identified and offered fracture risk assessment. For elderly in-patients with fractures of hip, vertebrae, a total of two or more fragility fractures, or 10-year probability of MOF ≥ 20% calculated using FRAX, the treatment decision was made without the need of DXA scan (n = 1235). The participants were recruited among those who were referred to DXA (n = 1447), of whom 839 consented to participate in the study, 675 women and 164 men [23]. We included a total of 496 women who all had responded to a questionnaire on risk factors for fracture, had valid measurement of TBS, and BMD of the femoral neck and lumbar spine, and 423 of them had VFA performed. No patients were excluded due to conditions known to affect bone metabolism, such as chronic kidney disease, use of anti-osteoporosis drugs, HRT, or premenopausal status. The study was approved by The Regional Committee for Medical and Health Research Ethics (REK 2014/2260).

Variables

The index fractures leading to inclusion were fragility fractures of the forearm (n = 196), ankle (n = 90), proximal humerus (n = 68), hip (n = 36), vertebrae (thoracic and lumbar) (n = 23), and other sites (n = 83). No women had rib or cervical fractures as index fracture. The vertebral fractures that led to inclusion were diagnosed on x-ray, CT, or MRI, not by VFA. Information on number of fractures after the age of 50, number of falls during the last 12 months before inclusion, parental history of hip fractures (yes vs. no), comorbidity, medication, postmenopausal status (yes vs. no), age at menopause, number of children, total months of breastfeeding, smoking (yes vs. no), daily alcohol intake (yes vs. no), physical activity (h/week), and dairy products (units/day) were collected through a questionnaire.

Height and weight was measured without shoes and heavy clothing, and BMI was calculated as weight per square meter height. BMD was measured at the lumbar spine (L1–L4), femoral neck, and total hip at both sides and using DXA Prodigy Pro in Tromsø and iDXA Pro in Drammen (both GE Lunar, Madison, WI, USA). Phantom Quality Assurance (QA) of the DXA equipment was performed daily. All fractured lumbar vertebrae were excluded, and BMD T-scores at femoral neck and total hip were calculated using the Third National Health and Nutrition Examination Survey with reference data of female Caucasians aged 20–29 years [26]. iNsight software (MediMaps, Geneva, Switzerland) version 3.0.1 was used to calculate TBS values from the DXA scans used for lumbar spine BMD (L1–L4), and fractured vertebrae were excluded. European (Medimaps) reference population was used.

Lateral images of the thoracolumbar spine (T4–L4) were obtained from DXA scans with the patient in a lateral decubitus position with lumbar support and hips flexed 90 degrees. An experienced physician (TTB) performed VFA and grading of the fracture severity using Genant's method for the semiquantitative (SQ) vertebral fracture scoring [27]. This combines the visual identification of fracture of vertebral bodies (height loss of the anterior, middle, posterior, or the whole vertebra) and grading of the fracture by percentage of height loss. A SQ score of 0 (SQ0) (< 20% height loss) is a non-fractured vertebra, SQ1 (20–25% height loss) a mild fracture, SQ2 (25–40% height loss) a moderate fracture, and SQ3 (≥ 40% height loss) a severe fracture. We classified the presence of one or more SQ1, SQ2, or SQ3 fractures as SQ1–SQ3 fractures, one or more SQ2 or SQ3 fractures as SQ2–SQ3 fractures, and presence of at least one SQ3 fracture as ≥ SQ3. The inter-observer agreement of SQ1–SQ3 fractures tested against another experienced clinician showed a κ of 0.84 (95% CI 0.70, 0.98) [23].

Statistical analyses

Characteristics of the cohort were calculated as mean ± standard deviation (SD) for the continuous variables and number with percentages (%) for categorical variables. Continuous variables were checked for normality using quantile-quantile (QQ) plot. All these variables were normally distributed except breastfeeding which was log-transformed in further analyses. Scatterplots were performed between continuous variables and visually checked for linearity. Univariable linear regression analyses were performed to investigate associations between the outcome variable TBS and clinical relevant determinants (age, BMI, history of prior fractures after the age of 50, falls during the last 12 months before inclusion, parental

history of hip fractures, comorbidities, use of medications, number of children, breastfeeding, currently smoking, daily alcohol consumption, physical activity, consumption of dairy products, prevalence of SQ1–SQ3 fractures, femoral neck and lumbar spine BMD). Only determinants significant at p-level < 0.10 were retained and included in multivariable models. Multiple linear regression analyses were performed, and because of potential multi-collinearity between TBS, femoral neck, and lumbar spine BMD, we tested different models for each of the traits to explore the attributional variance in the outcome variable by the introduced determinants. Non-significant determinants were removed one by one until the exposure variables with statistical significant association remained ($p < 0.05$). Determinants that had been removed were reintroduced one by one to re-check for significance. Results are presented as β coefficients with 95% confidence intervals (CIs), p values, and explained variance (R^2). The same procedure was performed with femoral neck and lumbar spine BMD as outcome variables. Univariable logistic regression analyses were performed to explore associations between SQ1–SQ3 fractures (yes vs. no) as the outcome variable and the determinants used in the linear regression models (listed above). Variables with significant association at p level < 0.10 were included in the multivariable logistic regression analyses. We tested different models including TBS, femoral neck, and lumbar spine BMD as determinants to evaluate the association with SQ1–SQ3 fractures. Determinants without significant association with the outcome SQ1–SQ3 fractures were removed one by one until the final model contained only the exposure variables with significant association ($p < 0.05$). Then, the removed variables were reintroduced one by one to re-check for significance. Results are presented by odds ratio (OR) with 95% CI. Evaluation of the predictive accuracy of the models was assessed by calibration and discrimination. Calibration was evaluated by the Hosmer and Lemeshow goodness-of-fit test. A statistically non-significant Hosmer and Lemeshow result ($p > 0.05$) suggests that the fit of the model is acceptable. Discrimination of SQ1–SQ3 fractures was evaluated by analysis of the area under the receiver operating characteristic (ROC) curve. We defined acceptable discriminatory capability as an area under the ROC curve greater than 0.7. Standardized regression coefficients ($\beta_{\text{per SD}}$) or odds ratio ($OR_{\text{per SD}}$) with 95% CI was used to facilitate the comparison of the strength of the associations between the continuous exposure variables and the outcome variables. The number of determinants in the multiple linear regression models did not exceed 10% of the number of observations. The number of determinants in the multiple logistic regression models never exceeded 14, as there were 141 SQ1–SQ3 fractures (maximum 10 events per determinant). All analyses were performed using Stata v15 (Version 15, StataCorp LP, TX, USA).

Results

The mean age of the 496 women was 65.6 years (± 8.6) and 193 (42.1%) women had sustained one or more fractures prior to the index fracture after the age of 50 (Table 1). One in three exhibited SQ1–SQ3 fractures on VFA. Mean TBS was 1.27 and BMD at femoral neck, total hip, and lumbar spine was 0.795 g/cm^2, 0.835 g/cm^2, and 1.027 g/cm^2, respectively. The mean number of falls during the last 12 months prior to

Table 1 Characteristics of 496 women 50 years and older with a recent fragility fracture

	Number	Total
Age, years	496	65.6 ± 8.6
Body mass index, kg/m^2	496	26.1 ± 4.0
History of prior fracture after age of 50	459	193 (42.1)
Number of falls during the last 12 months	489	1.3 ± 0.7
Parental history of hip fracture	410	100 (24.4)
Ulcus/gastritis	476	56 (11.8)
Asthma/COLD	489	53 (10.8)
Type 1 and type 2 diabetes	495	23 (4.6)
Rheumatoid arthritis	488	22 (4.5)
Myocardial infaction	496	13 (2.6)
Cancer	495	71 (14.3)
Hypothyreosis	490	54 (11.2)
Hyperthyreosis	490	13 (2.7)
Use of antacids	483	76 (15.7)
Use of statins	488	119 (24.4)
Use of oral glucocorticoids	486	28 (5.8)
Menopausal estrogen supplementation	436	29 (6.7)
Use of AOD at baseline	446	41 (9.2)
Postmenopausal status	447	429 (96.0)
Age at menopause, years	399	48.7 ± 4.9
Number of children	432	2.2 ± 1.2
Nullipara	432	34 (7.8)
Breastfeeding, months[a]	325	10 (0 – 96)
No breastfeeding	325	45 (13.9)
Currently smoking	479	71 (14.8)
Daily alcohol intake	487	48 (9.8)
Physical activity, h/week	454	2.8 ± 1.8
Intake of dairy products, units/day	480	2.3 ± 1.1
Trabecular bone score lumbar spine	496	1.27 ± 0.10
SQ1-SQ3 fracture	423	141 (33.3)
Femoral neck BMD, g/cm^2	482	0.795 ± 0.105
Total hip BMD, g/cm^2	482	0.835 ± 0.118
Lumbar spine BMD, g/cm^2	496	1.027 ± 0.166
Lowest BMD any site, T-score	496	− 2.1 ± 0.9

COLD chronic obstructive lung disease, *AOD* anti-osteoporosis drugs, *SQ* vertebral fractures assessed by semiquantitative method, *BMD* bone mineral density

Values are mean ± SD or *n* (%), except [a] median (range)

inclusion was 1.3, about one in four women reported a history of parental hip fracture, and one in ten reported daily alcohol intake. The women had on average given birth to 2.2 children (including the 7.8% of the women who were nulliparous). The median duration of total time of breastfeeding was 10 months (range 0–96 months).

Determinants of TBS

Higher age ($\beta_{per\ SD} = -0.26$, 95% CI −0.36, −0.15), a history of parental hip fracture (β = −0.29, 95% CI −0.54, −0.05), and daily alcohol intake (yes vs. no) (β = −0.43, 95% CI −0.79, −0.08) were associated with a lower TBS (Table 2; Fig. 1). Higher age at menopause ($\beta_{per\ SD}$ = 0.11, 95% CI 0.01, 0.21), higher BMD of the femoral neck ($\beta_{per\ SD}$ = 0.34, 95% CI 0.25, 0.43), and lumbar spine ($\beta_{per\ SD}$ = 0.40, 95% CI 0.31, 0.48) were associated with higher TBS. In models additionally including SQ1–SQ3 fractures, femoral neck or lumbar spine BMD, age at menopause were no longer associated with TBS. SQ1–SQ3 fractures were not associated with TBS in models including age and daily alcohol consumption. Replacing SQ1–SQ3 fractures with SQ2–SQ3 fractures or SQ3 fractures in multivariable analyses did not change the results. The model including the significant determinant age, parental hip fracture, daily alcohol consumption, number of children, and lumbar spine BMD explained 28% of the variance in TBS. Femoral neck BMD explained 8% and lumbar spine BMD 18% of the variance in TBS.

Determinants of SQ1–SQ3 fractures

Age ($OR_{per\ SD}$ = 1.94, 95% CI 1.51–2.46) and a history of prior fractures (OR = 1.71, 95% CI 1.09–2.71) were positively associated with SQ1–SQ3 fractures (Table 3). Lumbar spine BMD ($OR_{per\ SD}$ = 0.75 95% CI 0.60–0.95) was negatively associated with SQ1–SQ3 fractures in models including age and prior fracture. SQ1–SQ3 fractures were neither associated with TBS nor femoral neck BMD in models including age and prior fractures. In analyses with SQ2–SQ3 fractures and SQ3 fractures as outcome variables, the results were similar.

Determinants of femoral neck BMD

Higher age ($\beta_{per\ SD}$ = −0.35, 95% CI: −0.43, −0.27) was associated with lower femoral neck BMD, while higher BMI ($\beta_{per\ SD}$ = 0.28, 95% CI: 0.20, 0.36) and higher TBS ($\beta_{per\ SD}$ = 0.32, 95% CI: 0.25, 0.40) were associated with higher femoral neck BMD (Table 4). Age, BMI, myocardial infarction, and TBS explained 32% of the variance in femoral neck BMD. TBS explained 10% of the variance in femoral neck BMD.

Table 2 Association between risk factors for fracture and 1 standard deviation (SD) difference in trabecular bone score (TBS)

	Univariable analyses		Multivariable model[a]		Model[a] + SQ1-SQ3		Model[a] + femoral neck BMD		Model[a] + lumbar spine BMD	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Age per SD	−0.29 (−0.37, −0.20)	< 0.001	−0.26 (−0.36, −0.15)	< 0.001	−0.25 (−0.35,−0.15)	< 0.001	−0.16 (−0.24, −0.07)	0.001	−0.24 (−0.32, −0.15)	< 0.001
BMI per SD	0.07 (0.02, 0,16)	0.116								
History of prior fracture	−0.19 (0.37, 0.01)	0.038								
Parental hip fracture	−0.25 (−0.47, −0.03)	0.028	−0.29 (−0.54, −0.05)	0.017					−0.28 (−0.48, −0.07)	0.008
Using AOD at baseline	−0.32 (−0.64, −0.00)	0.047								
Age at menopause per SD	0.08 (−0.02, 0.18)	0.099	0.11 (0.01, 0.21)	0.036						
Number of children	0.08 (−0 00, 0.16)	0.058							0.09 (0.01, 0.17)	0.036
Daily alcohol consumption	−0.33 (−0.63, −0.03)	0.030	−0.43 (−0.79, −0.08)	0.017	−0.47 (−0.76, −0.17)	0.002	−0.32 (−0.60, −0.04)	0.027	−0.41 (−0.70, −0.12)	0.006
SQ1– SQ3 fractures	−0.31 (−0.50, −0.11)	0.003	–	–	−0.14 (−0.34, 0.07)	0.184	–		–	–
Femoral neck BMD per SD	0.41 (0.33, 0.50)	< 0.001	–	–	–	–	0.34 (0.25, 0.43)	< 0.001	–	–
Lumbar spine BMD per SD	0.44 (0.36, 0.52)	< 0.001	–	–	–	–	–	–	0.40 (0.31, 0.48)	< 0.001
R^2	–		0.11		0.09		0.19		0.29	

SQ vertebral fractures assessed by semiquantitative method, *BMD* bone mineral density, *β* beta coefficient in linear regression analysis, *CI* confidence interval

[a] Including age, BMI (body mass index), prior fracture, parental hip fracture, using AOD at baseline, age at menopause, number of children and daily alcohol intake. Only significant results are shown

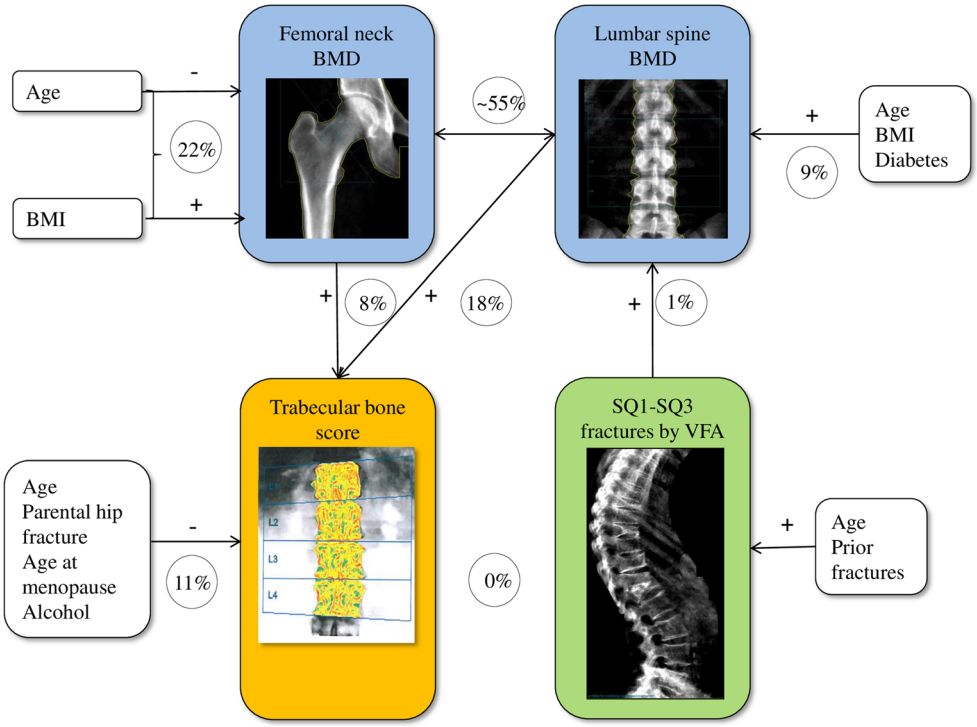

Fig. 1 Associations between femoral neck and lumbar spine bone mineral density (BMD), trabecular bone score (TBS) and vertebral fractures on VFA (SQ1-SQ3) with attributed variance of their determinants. *BMI* body mass index

Determinants of lumbar spine BMD

SQ1–SQ3 fractures ($\beta_{per\ SD} = -0.25$, 95% CI −0.43, −0.07) were associated with a lower lumbar spine BMD, while higher age ($\beta_{per\ SD} = 0.20$, 95% CI 0.12, 0.29), higher BMI ($\beta_{per\ SD} = 0.20$, 95% CI 0.12, 0.29), diabetes ($\beta = 0.61$, 95% CI: 0.21, 1.00) and high TBS ($\beta_{per\ SD} = 0.43$, 95% CI 0.34, 0.51) were associated with higher lumbar spine BMD (Table 5). TBS and SQ1–SQ3 fractures explained 17% and 1% of the variance in lumbar spine BMD, respectively.

Discussion

No association between TBS and SQ1–SQ3 fractures could be demonstrated in this cohort of women with prevalent fragility fractures. We found that higher age, a history of parental hip fracture, and daily alcohol consumption were associated with lower TBS, while higher femoral neck and lumbar spine BMD were associated with higher TBS. Age and prior fractures were positively associated with SQ1–SQ3 fractures, whereas lumbar spine BMDs were negatively associated with SQ1–SQ3 fractures.

The unexpected finding of no association between TBS and SQ1–SQ3 fractures has previously been shown in a study of elderly Swedish women with prevalent vertebral fractures [20] and in men in the Manitoba study and MrOs study with incident vertebral fractures [21, 22]. There are other studies showing an association between TBS and SQ1–SQ3 fractures in women [18, 19]. We do not know why these findings diverge between studies, but several factors may be of importance. Firstly, genetic factors explain a large part of the variation in TBS and vertebral fractures, and genetic factors may vary significantly between countries and the cohorts studied. Scandinavian women are a genetically homogenous group, and they have the highest prevalence of vertebral fractures in Europe [28]. Secondly, TBS is derived from the same images as lumbar spine BMD. Lumbar spine BMD accounted for a larger contribution to the variance of TBS (20%) than femoral neck BMD (10%) in our cohort. SQ1–SQ3 fractures were negatively associated with lumbar spine BMD, and only about 1% of the variance in lumbar spine BMD was explained by SQ1–SQ3 fractures, suggesting a weak association. No association between SQ1–SQ3 fractures and femoral neck BMD was found. We might infer that in our cohort of women with fragility fractures, SQ1–SQ3 fractures reflect reduced bone strength that is not captured by BMD nor TBS.

The determinants of TBS identified in our study differ somewhat from what was found in the population-based Canadian Manitoba study [10]. We found a negative association of TBS with age and daily alcohol intake, but no associations with BMI, glucocorticoid use, rheumatoid arthritis, or chronic obstructive pulmonary disease. This could be due to the smaller sample size in our study compared to the Manitoba study (496 vs. 29,407) or that the source of the data differed. We collected self-reported information on lifestyle, comorbidities, and medication, with limitations regarding self-reported data (i.e. possible information bias). In the Manitoba study, this information was retrieved from register-based data of physician billing claims, hospital discharge abstracts, and

Table 3 Odds ratio (OR) of presence of SQ1-SQ3 fractures (yes vs. no) with possible risk factors for fracture

	Univariable analyses		Multivariable model[a]		Model[a] + TBS		Model[a] + femoral neck BMD		Model[a] + lumbar spine BMD	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age per SD	2.02 (1.60,2.56)	< 0.001	1.94 (1.51, 2.46)	< 0.001	1.86 (1.44, 2.40)	< 0.001	1.87 (1.43, 2.45)	< 0.001	1.93 (1.49, 2.48)	< 0.001
BMI per SD	1.08 (0.89, 1.32)	0.437								
History of prior fracture	2.37 (1.54, 3.64)	< 0.001	1.71 (1.09, 2.71)	0.021	1.71(1.08, 2.70)	0.022	1.66 (1.04, 2.65)	0.033	1.76 (1.11, 2.79)	0.017
Cerebrovascular event	4.20 (1.24, 14.19)	0.021								
TBS per SD	0.73(0.59, 0.90)	0.003	–	–	0.81 (0.64, 1.03)	0.084	–		–	–
Femoral neck BMD per SD	0.70 (0.56, 0.87)	0.002	–	–	–	–	0.91 (0.71, 1.16)	0.452	–	–
Lumbar spine BMD per SD	0.70 (0.56, 0.87)	0.002	–	–	–	–	–		0.75 (0.60, 0.95)	0.017

TBS trabecular bone score, *BMD* bone mineral density, *CI* confidence interval

[a] Including age, BMI (body mass index), prior fracture, and cerebrovascular accident. Only significant or important results are shown

Table 4 Association between risk factors for fracture and 1 standard deviation (SD) difference in femoral neck bone mineral density (BMD)

	Univariable analyses		Multivariable model[a]		Model[a] + TBS		Model[a] + SQ1-SQ3		Model[a] + SQ1-SQ3 + TBS	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Age per SD	− 0.38 (− 0.46, − 0.30)	< 0.001	− 0.35(− 0.43,− 0.27)	< 0.001	− 0.26 (− 0.33, − 0.17)	< 0.001	− 0.30 (− 0.40, − 0.21)	< 0.001	− 0.26 (− 0.33, − 0.18)	< 0.001
BMI per SD	0.31 (0.23, 0.40)	< 0.001	0.28 (0.20, 0.36)	< 0.001	0.27 (0.20, 0.35)	< 0.001	0.28 (0.20, 0.37)	< 0.001	0.27 (0.20, 0.35)	< 0.001
Prior fracture	− 0.30 (− 0.49, − 0.12)	0.002								
Asthma/COLD	− 0.34 (− 0.62, − 0.05)	0.021								
Myocardial infarction	− 0.62 (− 1.19, − 0.05)	0.035			− 0.50 (− 0.98, − 0.03)	0.039	− 0.60(− 1.14, − 0.06)	0.029	− 0.50 (− 0.98, − 0.03)	0.039
Using AOD at baseline	− 0.51 (− 0.83, − 0.19)	0.002					− 0.34 (− 0.66, − 0.02)	0.040		
TBS per SD	0.41 (0.33, 0.49)	< 0.001	–	–	0.32 (0.25, 0.40)	< 0.001	-	–	0.29 (0.20, 0.38)	< 0.001
SQ1-SQ3 fractures	− 0.33 (− 0.53, − 0.13)	0.001	–	–	–	–	− 0.20 (− 0.39, 0.00)	0.051	− 0.12 (− 0.30, 0.05)	0.173
Lumbar spine BMD per SD	0.57 (0.49, 0.64)	< 0.001	–	–	–	–	–	–	–	–
R^2	–		0.22		0.32		0.25		0.31	

TBS trabecular bone score, *SQ* vertebral fractures assessed by semiquantitative method, *β* beta coefficients in linear regression analysis, *CI* confidence interval, *COLD* chronic obstructive lung disease, R^2 explained variance

[a] Including age, BMI (body mass index), prior fracture, asthma/COLD, myocardial infarction and previous AOD (anti-osteoporosis drugs). Only significant results are shown

Table 5 Association between risk factors for fracture and 1 standard deviation (SD) difference in lumbar spine bone mineral density (BMD)

	Univariable analyses		Multivariable model[a]		Model[a] + TBS		Model[a] + SQ1-SQ3		Model[a] + SQ1-SQ3 + TBS	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Age per SD	− 0.14 (− 0.22, − 0.05)	0.003	− 0.12 (− 0.21, − 0.03)	0.006					0.09 (0.00, 0.18)	0.045
BMI per SD	0.24 (0.15, 0.32)	< 0.001	0.22 (0.13, 0.30)	< 0.001	0.19 (0.12, 0.27)	< 0.001	0.24 (0.15, 0.33)	< 0.001	0.20 (0.12, 0.29)	< 0.001
Falls[b] per SD	− 0.10 (− 0.22, 0.02)	0.088	− 0.12 (− 0.23, − 0.00)	0.049						
Diabetes	0.60 (0.19, 1.02)	0.005	0.51 (0.10, 0.92)	0.014	0.65 (0.28, 1.02)	0.001	0.44 (0.02, 0.87)	0.042	0.61 (0.21, 1.00)	0.003
Rheumatoid arthritis	0.40 (− 0.06, 0.80)	0.092								
Smoking	0.23 (− 0.03, 0.48)	0.079								
TBS per SD	0.44 (0.36, 0.52)	< 0.001	–		0.44 (0.36, 0.51)	< 0.001	–	–	0.43 (0.34, 0.51)	< 0.001
SQ1-SQ3 fractures	− 0.32 (− 0.52, − 0.12)	0.001	–		–	–	− 0.33 (− 0.52, − 0.14)	0.001	− 0.25 (− 0.43, − 0.07)	0.008
FN BMD per SD	0.54 (0.47, 0.61)	< 0.001	–		–	–	–	–	–	–
R^2	–		0.09		0.25		0.10		0.26	

TBS trabecular bone score, *SQ* vertebral fractures assessed by semiquantitative method, *β* beta coefficients in linear regression analysis, *CI* confidence interval, *FN* femoral neck

[a] Including age, BMI (body mass index), falls, diabetes, rheumatoid arthritis and smoking. Only significant results are shown

[b] Number of falls the last 12 months prior to inclusion

provincal retail pharmacy database, with uncertainities regarding the validity of registered information (i.e. whether the discharge record reflects the disease at hand). Both studies reported a positive association between femoral neck and lumbar spine BMD and TBS. The variance in TBS explained by femoral neck and lumbar spine BMD in the Manitoba women was 7% and 11%, respectively, compared to 20% and 28% in the NoFRACT women. This might be explained by the inclusion of healthier subjects in the Manitoba cohort where only 14% had a previous major fracture, compared to the NoFRACT cohort, where all the women had a clinical fragility fracture. In addition, patients with BMI > 37 kg/m^2 were not excluded in the Manitoba study, which may have diluted the association between BMD and TBS.

We found higher OR for SQ1–SQ3 fractures in patients with a history of a prior fracture, increasing age and decreasing lumbar spine BMD, in line with other studies [29–31]. No association between SQ1–SQ3 fractures and body weight or BMI was found in adjusted models, which is in accordance with some studies [29–31], but contrary to others [32, 33]. Studies on incident vertebral fractures, however, show similar results. In the EPOS study, including 3402 women, late menarche (after 16 years of age) was associated with an increased risk of incident vertebral fracture, whereas HRT, increasing body weight, and BMI were protective [16]. Lifestyle factors such as smoking, alcohol intake, physical activity, or milk consumption showed no association with incident vertebral fractures, in line with our findings in patients with prevalent vertebral fractures. In the prospective population-based Rotterdam Study including 2467 women, age, low BMD, prevalent vertebral fractures, early menopause (< 45 years of age), currently smoking, and walking aid use were associated with incident vertebral fractures in women [15]. Prevalent and incident vertebral fractures are not comparable, although the risk factors should be similar.

To the best of our knowledge, this is the first study on determinants of TBS in a cohort of women with fragility fractures. However, there are some limitations. The study sample was perhaps too small to show associations with the main outcome variables (TBS, SQ1–SQ3 fractures) and certain risk factors, such as glucocorticoid use, rheumatoid arthritis, and chronic obstructive pulmonary disease. On the other hand, we showed that more of the variance in TBS could be explained by BMD than in the Manitoba study, maybe due to exclusion of obese patients or the selection of patients who all had suffered at least one fragility fracture. As a result of the cross-sectional design, it was not possible to determine the temporal nature of any observed associations.

In conclusion, no statistical significant association between TBS and SQ1–SQ3 fractures was found. Higher age, a history of parental hip fracture, and daily alcohol consumption were associated with lower TBS, while higher femoral neck and lumbar spine BMD were associated with higher TBS. Age

and a history of prior fractures were positively associated with SQ1–SQ3 fractures, while lumbar spine BMD was negatively associated with SQ1–SQ3 fractures. Modifiable risk factors such as daily alcohol intake and low BMD are important targets in fracture prevention strategies. Since TBS and SQ1–SQ3 fractures are not associated, each of them may act as independent risk factors for fracture, justifying the use of both in post-fracture risk assessment.

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Compliance with ethical standards

The study was approved by The Regional Committee for Medical and Health Research Ethics (REK 2014/2260).

Conflicts of interest Tove T Borgen, Åshild Bjørnerem, Camilla Andreasen, Cathrine Brunborg, Lars M Hübschle, Ellen M Apalset, Jan-Erik Gjertsen, Trude Basso, Ida Lund, Ann Kristin Hansen, and Cecilie Dahl declare that they have no conflict of interest. Lene B Solberg has received speaker honorarium from Eli Lilly. May-Britt Stenbro has received speaker fees from Eli Lilly, Amgen, and Takeda. Wender Figved has received speaker fees from Ortomedic AS. Jens-Meinhard Stutzer has received grants for educational activities from BSN Medical. Lars Nordsletten has received speaker fees from Novartis, Eli Lilly, and Ortomedic AS. Frede Frihagen has received grants for educational activities from Eli Lilly, Amgen, and Takeda. Erik F Eriksen has received speaker fees from Novartis, Eli Lilly, Amgen, MSD, EffRx, IDS, and Shire.

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